“A PROSPECTIVE RANDOMISED STUDY COMPARING THE PRE-EMPTIVE ANALGESIC EFFECTS OF ORAL GABAPENTIN WITH ORAL CLONIDINE ON INTUBATION RESPONSE AND POST OPERATIVE ANALGESIC REQUIREMENT FOR PATIENTS UNDER GOING LAPAROSCOPIC CHOLECYSTECTOMY”

Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

In partial fulfilment for the award of the degree of

DOCTOR OF MEDICINE

IN

ANAESTHESIOLOGY

BRANCH X

INSTITUTE OF ANAESTHESIOLOGY AND CRITICAL CARE

MADRAS MEDICAL COLLEGE

CHENNAI- 600003

APRIL 2016

CERTIFICATE

This is to certify that the dissertation titled, **"A PROSPECTIVE RANDOMISED STUDY COMPARING THE PRE-EMPTIVE ANALGESIC EFFECTS OF ORAL GABAPENTIN WITH ORAL CLONIDINE ON INTUBATION RESPONSE AND POST OPERATIVE ANALGESIC REQUIREMENT FOR PATIENTS UNDER GOING LAPAROSCOPIC CHOLECYSTECTOMY"** is submitted by **Dr. C.KOKILA** in partial fulfilment for the award of the degree of **DOCTOR OF MEDICINE** in **ANAESTHESIOLOGY** by The Tamilnadu Dr.M.G.R medical university, Chennai is a bonafide record of work done by him in the **INSTITUTE OF ANAESTHESIOLOGY& CRITICAL CARE**, Madras Medical College, during the academic year **2013 -2016** .

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CERTIFICATE OF THE GUIDE

This is to certify that the dissertation titled, **"A Prospective, randomized study comparing the pre-emptive analgesic effects of oral Gabapentin with oral Clonidine on intubation response and postoperative analgesic requirement for patients undergoing Laparoscopic Cholecystectomy"** is a bonafide research work done by **Dr. C. KOKILA ,** in partial fulfilment for the award of the degree of Doctor of Medicine in Anaesthesiology by the Tamil Nadu Dr. M.G.R. Medical University, Chennai., is a bonafide record of the work done by her in the **INSTITUTE OF ANAESTHESIOLOGY AND CRITICAL CARE, Madras Medical College** and government hospital, during the academic year **2013-2016**.

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DECLARATION

I hereby declare that the dissertation titled, **"A PROSPECTIVE RANDOMISED STUDY COMPARING THE PRE-EMPTIVE ANALGESIC EFFECTS OF ORAL GABAPENTIN WITH ORAL CLONIDINE ON INTUBATION RESPONSE AND POST OPERATIVE ANALGESIC REQUIREMENT FOR PATIENTS UNDER GOING LAPAROSCOPIC CHOLECYSTECTOMY"** has been prepared by me in the Institute of Anaesthesiology and Critical Care, Madras Medical College and Government General Hospital, Chennai, during the period 2013 – 2016 under the guidance of **DR. B.KALA, M.D., D.A.,** Director, Institute of Anaesthesiology and Critical Care, Madras Medical College, Chennai – 3 and submitted to **The Tamil Nadu Dr. M.G.R. Medical University, Guindy, Chennai – 32**, in partial fulfilment for the requirements for the award of the degree of M.D. Anaesthesiology (Branch X), examinations to be held on April 2016.

I have not submitted this dissertation previously to any journal or any university for the award of any degree or diploma.

Date:

Place: Chennai DR.C.KOKILA

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CONTENTS

ABSTRACT

AIM OF THE STUDY:

This study compares the pre-emptive analgesic effects of oral Gabapentin and oral Clonidine on intubation response and post-operative analgesic requirement for patients undergoing Laparoscopic Cholecystectomy.

ABSTRACT:

Pre-emptive Analgesia has been reported to provide good perioperative outcomes using various methods, in attenuating the hemodynamic response to intubation & laryngoscopy and decreasing the post-operative analgesic requirement in patients undergoing Laparoscopic Cholecystectomy. There has been very few studiesusing oral gabapentin and oral clonidine as pre-emptive analgesia In this study we randomly selected 75 patients and divided into three groups. Group A received oral Gabapentin of 900 m , Group B received oral Clonidine of 0.2 mg and Group C received oral Vitamin C , 90 minutes prior to induction.The primary outcomes were to measure the hemodynamic stress response by Heart Rate, Systolic blood pressure, Diastolic blood pressure, Mean arterial pressure during intubation and post-operative VAS score and Analgesic requirement.

RESULTS:

Heart rate, Systolic blood pressure, Diastolic blood pressure, Mean arterial pressure changes were lower with Clonidine than Gabapentin than placebo group

Post-operative VAS score and analgesic requirement were found to be much lower in Gabapentin Group than clonidine than placebo group.

CONCLUSION:

From my study, I conclude that both Gabapentin and Clonidine when given orally 90 minutes prior to induction were found to be effective as good pre-emptive analgesics in decreasing the

hemodynamic stress response to laryngoscopy and intubation , with the added benefit p of providing post-operative pain relief also. Clonidine was found to be slightly better than Gabapentin in attenuating hemodynamic stress response to laryngoscopy and intubation. Gabapentin was found to be slightly better than clonidine in providing post-operative pain relief.

INTRODUCTION

Laryngoscopy and endotracheal intubation are powerful stimuli which can increase the sympathetic activity leading to tachycardia, hypertension and dysrhythmias.[34,20] These hemodynamic changes are associated with the release of catecholamine (cortisol, epinephrine and nor-epinephrine), which are prone to get aggravated with laparoscopy using CO_2 pneumo-peritoneum concomitantly.

Pre-emptive analgesia with Gabapentin and Clonidineblunt the stress response to anaesthetic and surgical stimuli, also reduce the narcotic and anaesthetic doses in the peri-operative period. This feature makes Clonidine or Gabapentin useful in the anaesthetic management of patients undergoing laparoscopic surgeries.

Accordingly, this study was designed to compare the pre-emptive analgesia of oral Gabapentin and Clonidine in attenuating the haemodynamic response to intubation and decreasing the post-operative pain in patients undergoing laparoscopic cholecystectomy.

AIM OF THE STUDY

To compare the effects of Oral Gabapentin vs Oral Clonidine given as a pre-emptive analgesic, on attenuation of the intubation response and postoperative analgesic requirement in patients undergoing Laparoscopic Cholecystectomy.

Objectives:

- Haemodynamic changes with intubation
- Post-operative VAS score
- Post-operative analgesic requirement

PRE-EMPTIVE ANALGESIA

In 1913, the concept of Prevention of Pain, Pre-emptive Analgesia was first introduced by Crile.[34]

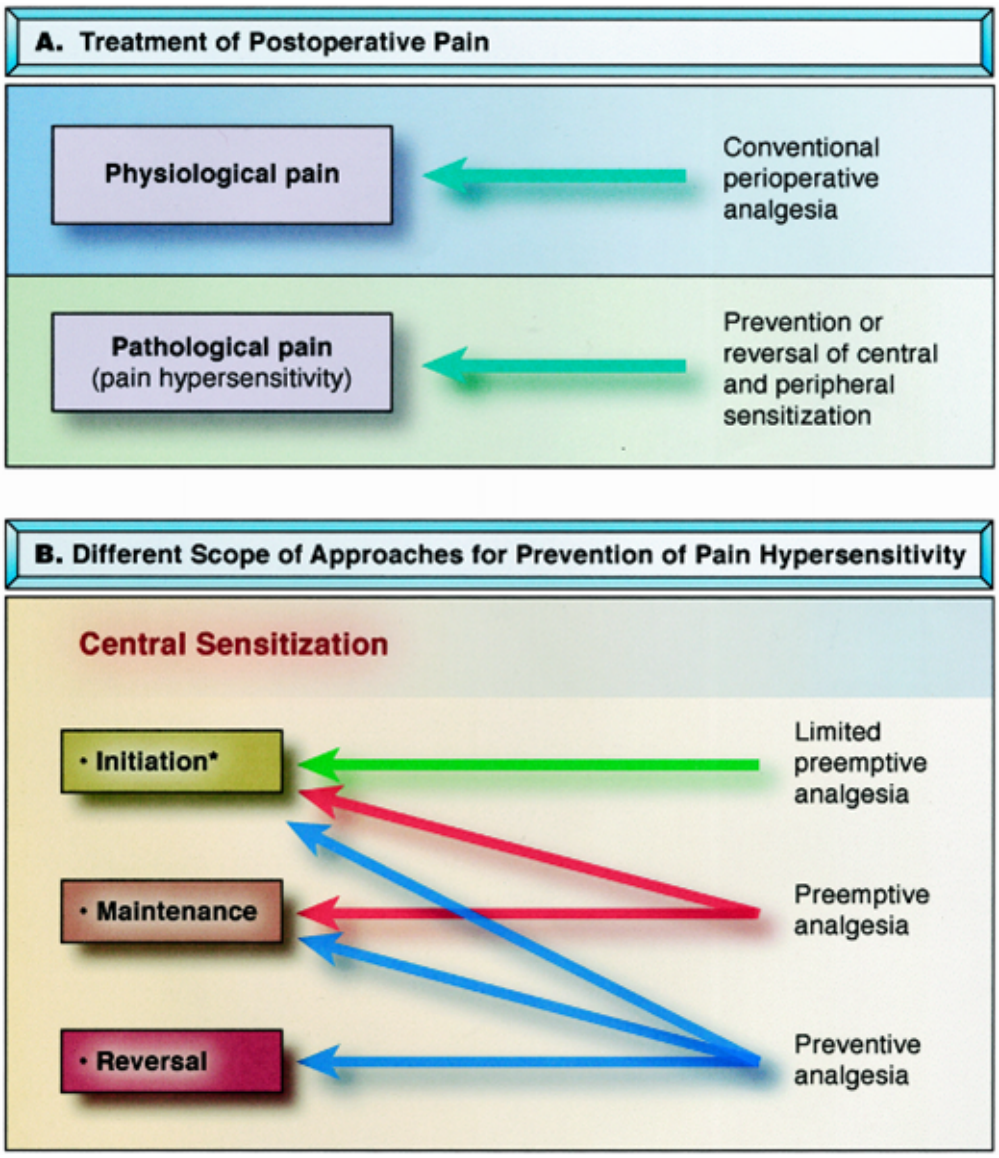
The first study on pre-emptive analgesia was published by Woolf and Wall in 1986.[56, 57]

Pre-emptive analgesia (PEA), the concept which initiated during the time of growing appreciation on features of pain pathway, is by administering effective analgesia prior to the anaesthetic and surgical trauma [56] Therapeutic choices for pre-emptive analgesia include almost all analgesic modalities and drugs individually or in combination. The primary assumption is that a pre-treatment approach diminishes acute pain scores and analgesic requirements more than post- surgical approach. Timing of the initiation and ability to inhibit sensitization are essential to the use of pre-emptive analgesia.[53]

Pre-emptive Analgesia is defined as "Treatment that prevents establishment of central sensitization caused by incisional and inflammatory injuries; the analgesic effect starts before incision and covers both the period of surgery and the initial postoperative period."

The balance between incisional injury and inflammatory injury depends on the nature of surgery; with inflammatory injury being a dominant factor.[58,19]

Pre-emptive analgesia inhibits (or reduces) pathologic pain that is different from physiologic pain in numerous ways.[15] It is excessive (in intensity and spread) and can be activated by low-intensity stimuli (allodynia, hyperalgesia) and hyperpathia.[15]



CONCEPT OF PRE-EMPTIVE ANALGESIA:

Pain sensation from damaged tissues, recruits a cascade of adaptations in somatosensory system leading to amplified responsiveness of both central and peripheral neurons. Because of these adaptations, response to subsequent stimuli is increased, thus escalating pain.

In pre-emptive analgesia, anti nociceptive treatment is started before and is operational during surgical procedure, so that the physiological consequences of

nociceptive transmission or reduced. Because of this protection on nociceptive pathways, pre-emptive analgesia is more effective than analgesic treatment initiated after surgery. Thereby pre-emptive analgesia reduces immediate postoperative pain and prevents the development of chronic pain.

SCIENTIFIC RATIOANLE:

Tissue damage is perceived by free nerve endings of peripheral nerves (first order neurons) called nociceptors. They act as transducers converting mechanical, chemical and thermal injury into electrical signals, which are then transmitted to dorsal horn neurons(second order neurons)in spinal cord.Nociceptors are of different forms; Myelinated Aδ nociceptors conduct rapid sharp well localised pain called first pain; Unmyelinated C nociceptors conduct duller, slower onset and poorly localised pain called second pain.

Dorsal horn contains two groups of neuron. Nociceptive specific (NS) neurons respond only to noxious stimuli from Aδ and C nociceptors.Wide dynamic range (WDR) neurons respond to both noxious stimuli and non noxious stimuli from Aβ fibres(i.e touch).Activity of WDR neurons depend on excitatory and inhibitory input from nociceptive and non nociceptive peripheral nerve fibres and descending inputs from supraspinal sites.

Tissue damage produces local inflammation by release of pain promoting substances (i.e. Substance P, prostaglandin, serotonin, bradykinin and histamine). They lead to peripheral sensitization of nociceptors which produce altered transduction and increased conduction of noxious impulses to CNS. Transmission of noxious stimuli from nociceptors to dorsal horn neurons(NS &WDR) effects in altered receptiveness of these neurons. Stimuli from Aδ and C fibres are amplified

(i.e. Hyperalgesia)and stimulus from Aβ fibres are misinterrupted. (i.e. allodynia). This is central sensitization.

Pre-emptive analgesia helps to prevent the neurological and biochemical consequences of noxious input to central nervous system.

CONCEPT OF PRE-EMPTIVE ANALGESIA[15]:

- Central hyperexcitability— exaggerated and prolonged responsiveness of neurons to normal afferent input after tissue damage
- Pre-incisional treatment — treatment that starts before an initial surgical incision
- Post-incisional treatment — treatment that starts immediately after the end of operation.

Noxious stimuli that are sufficient to induce injury to the tissue can cause hypersensitivity, hyperalgesia, allodyniaand abnormal paresthesia, which leads to initiation of pain by non-invasive stimulus. This is attributed to the combination of peripheral sensitization (associated with the lowered threshold of nociceptors) and central sensitization (related to the increased excitability of central nervous system).

These sensory disturbances are considered to the cause for persistent postoperative pain. Local tissue damage and inflammation along with various sympathetic terminal-derived chemical mediators (hydroxyl ions, noradrenaline, potassium ions, prostaglandins, purines, bradykinin, histamine, cytokines, 5-HT, leukotrienes, nerve growth factor and neuropeptides) are responsible for peripheral sensitization, which increases the excitability of dorsal horn neurons followed by central sensitization.

As soon as central sensitization is established, signals are transferred via Aβ fibers from low-threshold mechanoreceptors and are perceived as pain at dorsal horn neurons with high excitability. As Aδfibers and C fibers from the nociceptors are below peripheral sensitization, pain will be greater and are unremitting. Once central sensitization is established, patients respond poorly to analgesics.

Pre-emptive analgesia reduces postoperative pain by inhibiting central sensitization even before surgery, if pain is provided before surgery; central sensitization is inhibited and preventing postoperative hyperesthesia. Instead, if only postoperative analgesic treatment is delivered, surgery-induced central sensitization is established. Hence, postoperative hyperesthesia is only inhibited for the time being.

Many new studies on pre-emptive analgesia were published and it was found essential to consider the inflammatory injury for pain mechanism.

GOALS:

1. Reduction in acute pain after tissue injury.
2. Inhibits pain related pathologic modulation of central nervous system.
3. Prevents persistence of post-operative pain and development of chronic pain
4. Effective pre-emptive analgesia uses multiple pharmacological agents to diminish nociceptor activation by decreasing receptor activation and by inhibiting the activation of pain neurotransmitters.

HISTORY OF LARYNGOSCOPY AND INTUBATION

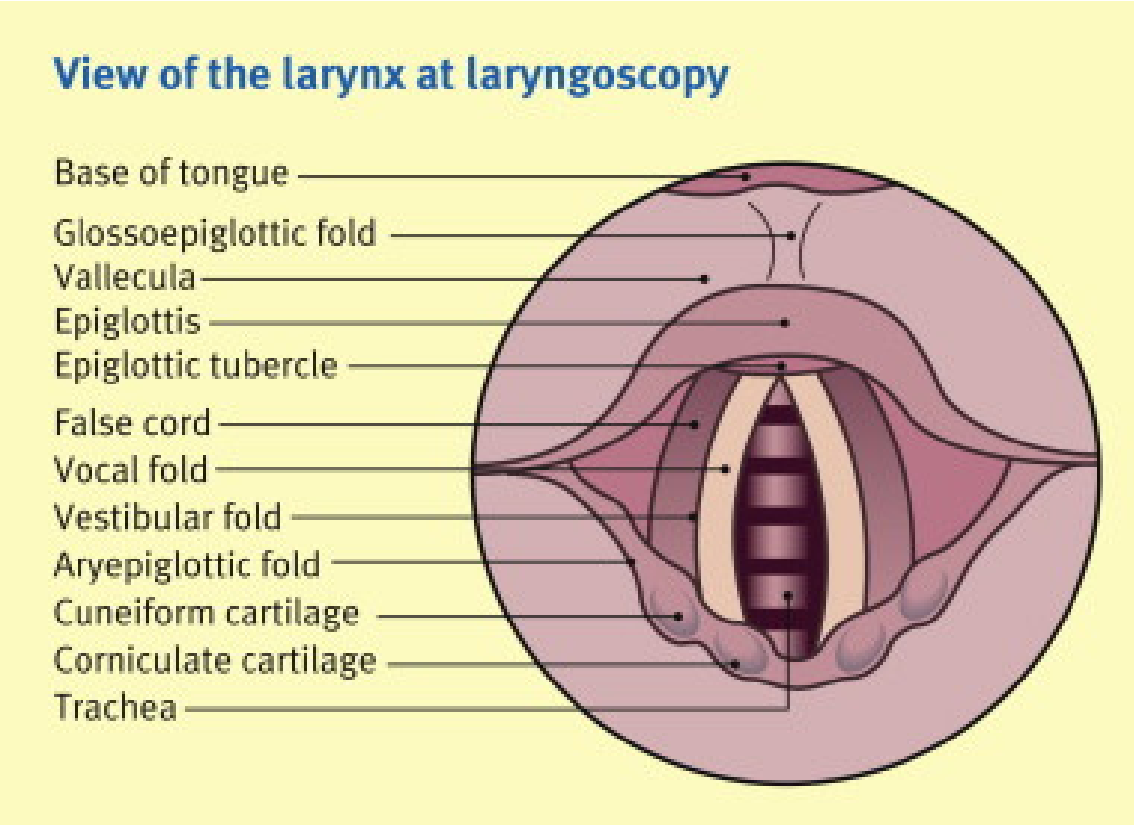
- In 1854, a Spanish vocal pedagogist, Manuel Garcia (1805-1906) was the first man to visualize the active glottis in a human being.
- On 23rd April 1895, the first direct laryngoscopy was performed by Alfred Kirsten.
- William Macewen (1848-1924) a Scottish Surgeon, conveyed orotracheal intubation as an alternative to tracheostomy.
- In 1913 Chevalior Jackson, has been recognised with high success in direct laryngoscopy.
- Sir Robert Macintosh (1897-1989), familiarised his new curved laryngoscopy blade in 1943.
- In 1940, Reid and Brace, was first to describe haemodynamic response to direct laryngoscopy and endotracheal intubation[34].

RESPONSE TO LARYNGOSCOPY

The induction of anaesthesia, laryngoscopy, tracheal intubation and surgical stimulation provoke cardiovascular responses leading to alteration in heart rate, cardiac rhythm and blood pressure. The response starts in 5 seconds, peaks in 1-2 minutes and returns to baseline in 5 minutes.

This sympatho-adrenal response is of little importance in healthy patients but dangerous in patients with hypertension, coronary artery disease, cerebrovascular disease, intracranial pathology, and hyperreactive airways, so it should be attenuated.[44,22]

Prof. King et al., in 1951 documented myocardial ischemic changes following laryngoscopy and intubation with increase in systolic blood pressure upto 40 mmHg even in normotensive patients.

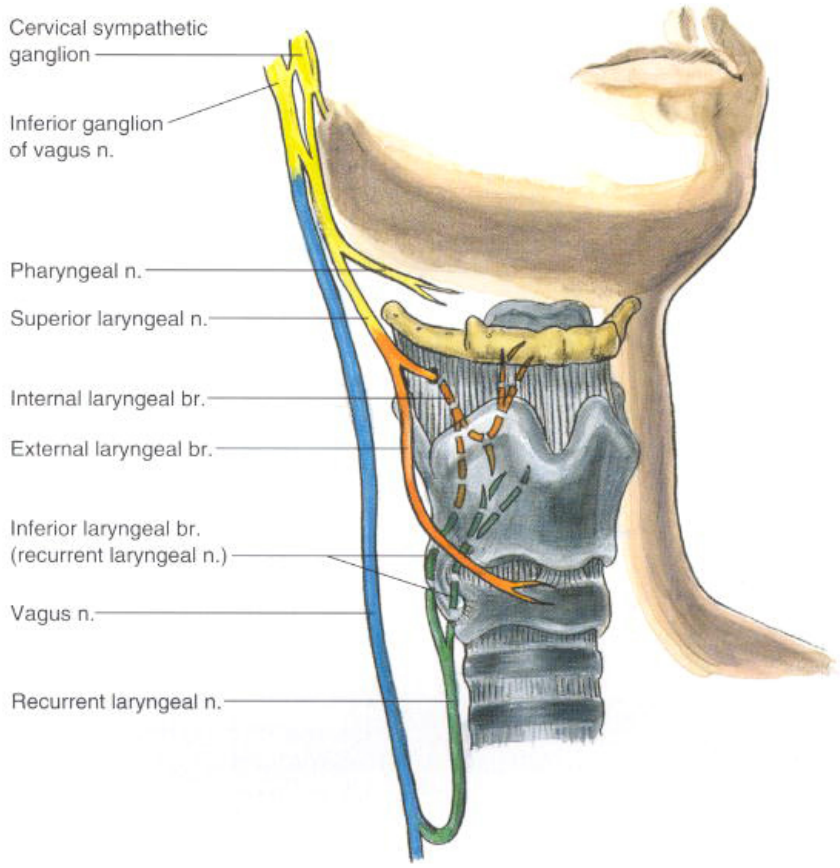


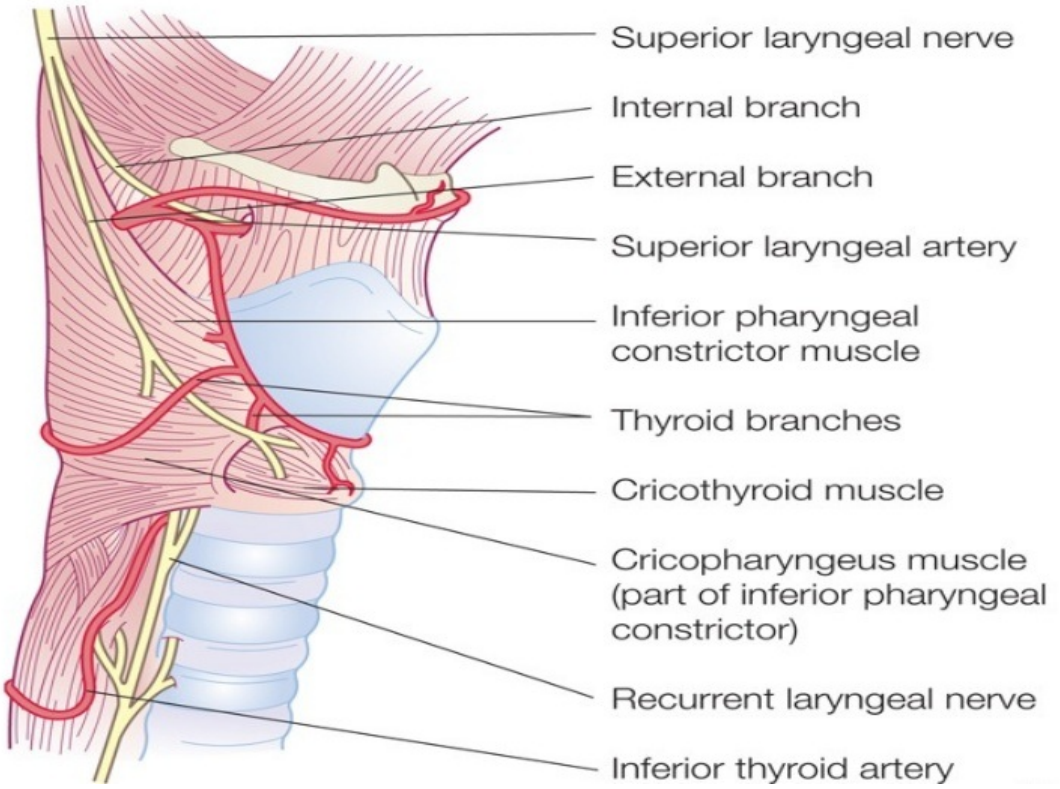
ANATOMY AND NERVE SUPPLY OF LARYNX

The pharynx is divided into nasopharynx, oropharynx and laryngopharynx. The oropharynx from laryngopharynx is separated by epiglottis.

The Hard and Soft palate is supplied by palatine branch of the trigeminal nerve.The anterior 2/3rd of the tongue is supplied by the lingual nerve and the posterior 1/3 rd of the tongue and the roof of the pharynx are supplied by glossopharyngeal nerve.

The pharyngeal surface of the epiglottis is supplied by the glossopharyngeal nerve and the laryngeal surface is supplied by the vagus. The sensory supply of the supraglottic area is by the internal branch of superior laryngeal nerve. The motor branch of the recurrent laryngeal nerve supplies all the intrinsic muscles of the larynx except the cricothyroid, which is supplied by the external laryngeal nerve and the sensory branches of the recurrent laryngeal nerve supply the mucosa of the larynx below the vocal cords.





PHYSIOLOGY OF THE STRESS RESPONSE:

The larynx is a highly innervated sensory structure, so laryngoscopy and tracheal intubation stimulates these structures leading to stress response.

Hemodynamic stress response to laryngoscopy and tracheal intubation augments as increase in heart rate and blood pressure due to reflex sympathetic discharge.[10] The subsequent rise in rate / pressure product may result in a myocardial oxygen demand which surpasses oxygen supply resulting in myocardial ischemia.This stress response starts within 5 seconds peaks within 10 minutes of intubation and returns to base line in 5 minutes.

The force and duration of laryngoscopy, hypoxia, hypercarbia, stimulation of carina by endotracheal tube, repeated and prolonged attempts are few factors which affect the stress response.

CARDIOVASCULAR RESPONSE:

Hypertension, tachycardia,bradycardia and dysrhythmias are mediated by autonomic nervous system. Hypertension, tachycardia, increase in cardiac work and oxygen consumption are mediated by sympathetic system via the cardio accelerator fibres and sympathetic chain ganglia. The polysynaptic pathway from 9^{th} to 10^{th} nerve afferents to sympathetic nervous system in the brain stem and spinal cord, results in a diffuse autonomic response, leading to extensive release of norepinephrine from the adrenergic terminals and release of epinephrine from the adrenal medulla.

Another reason, for the hypertensive response is due to activation of renin angiotensin system with release of renin from the renal juxtaglomerular apparatus and an end organ innervated by adrenergic nerve terminals.

Bradycardia which is caused by a rise in vagal tone in Sino Atrial node is a monosynaptic reflex to a noxious stimulus.

RESPIRATORY SYSTEM

- Possibility of Reflex glottis closure leading to laryngospasm,
- Dead space will be decreased.
- Airway resistance is increased
- Bronchospasm

STRESS RESPONSE IN PATHOLOGICAL CONDITIONS

1. Patients with limited myocardial reserve may go for myocardial ischemia and failure. So it is necessary to maintain the rate and blood pressure of the patient within 20% of the normal value. Heart rate should be less than 110 beats per minute (ischemic threshold)

2. Intracranial vascular anomalies can rupture.
3. In patients with hyperactive airways bronchospasm and laryngospasm can occur.
4. Laryngoscopy and intubation can increase cerebral blood flow if auto regulation is compromised. The resultant increase in intracranial pressure can lead to brainstem herniation and death.

Hemodynamic responses to laryngoscopy, intubation and laparoscopy should be diminished by the appropriate premedication, smooth induction, and rapid intubation. However, prevention and treatment of postoperative pain still remains a main challenge in postoperative care in spite of major advancements in pain assessment and therapy.

METHODS TO ATTENUATE INTUBATION RESPONSE

Hypertension and tachycardia have been reported as common during laryngoscopy and intubation in lighter plane of anaesthesia. Acceleration in blood pressure and heart rate occurs most commonly from reflex sympathetic discharge producing excessive catecholamines, which may be lethal in patients with heart disease and hypertension.[37, 49]

1. Maintaining a deep plane of general anaesthesia using volatile anaesthetics. This dose of volatile anaesthetics necessary to block the cardiovascular responses to endotracheal intubation may result in profound cardiovascular depression.The volatile agents used are Halothane, Isoflurane and Sevoflurane.
2. Local anaesthetics: Lignocaine is used.
    a. For oropharyngeal anaesthesia as viscous gargle
    b. Spray for intratracheal anaesthesia

c. Intravenous

d. Local instillation or topical spray over the vocal cords.

e. Regional nerve blocks.

3. Vasodilators – Nitroglycerine, sodium nitroprusside, hydralazine
4. Magnesium sulphate
5. Narcotics - Fentanyl, Sufentanyl,Remifentanyl, Morphine, Pethidine.

   Fentanyl is the most commonly used narcotic. It is a potent analgesic, has a short duration of action, and it does not increase intracranial tension with minimal circulatory changes.
6. Calcium Channel blockers – Nifidipine, Nicardipine, Verapamil, Diltiazem
7. Adrenergic blockers

   β Blockers – Metaprolol, Esmolol

   α Blocker - Phentolamine

   α and β blocker – Labetalol
8. Central Sympatholytics – Clonidine and Dexmeditomidine. They act by reducing central sympathetic outflow.
9. Sedatives and anxiolytics.

POST OPERATIVE PAIN ASSESSMENT METHODS:

In the post-operative period, assessing the degree of pain is very important. Assessing Pain is considered as an important vital sign in postoperative period. It must be done at regular intervals.

Post-operative pain assessment involves educating the patients to gain knowledge thereby alleviating the fear and anxiety about pain, which develops a positive approach towards pain, thereby improving the satisfaction of the patient.

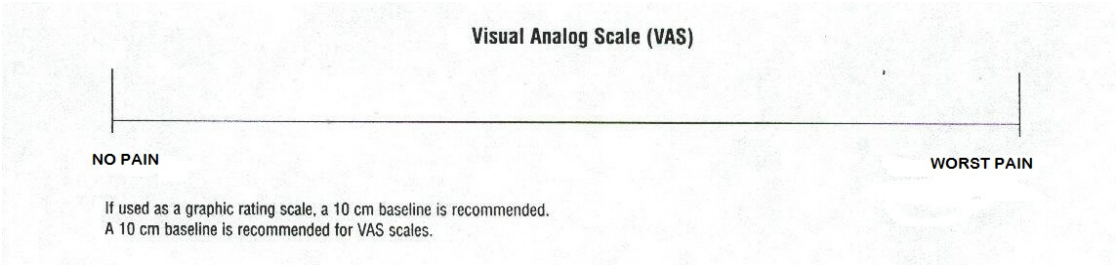
Pain assessment helps us to quantitate the intensity of pain, guides us to formulate analgesic regimen and to assess the response to treatment given. There are numerous methods to assess pain. These assessment methods need to be simple and easily understandable by the patient.

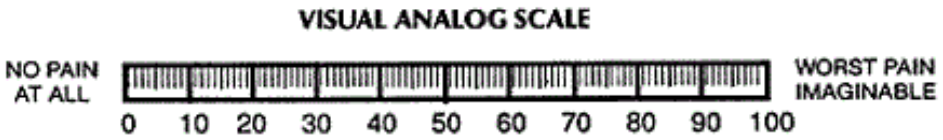
In patients who can communicate verbally, Self report is the gold standard and external signs of pain or distress (crying,wincing) are minor. For patients with difficulty in communication and in children, nonverbal indicators (behavioural and sometimes physiologic) may form the principal basis of information. Commonly used pain scales are:

- VISUAL ANALOG SCALE
- NUMERICAL RATING SCALE,
- VERBAL RATING SCALE
- WONG BAKER FACES RATING SCALE

VISUAL ANALOG SCALE

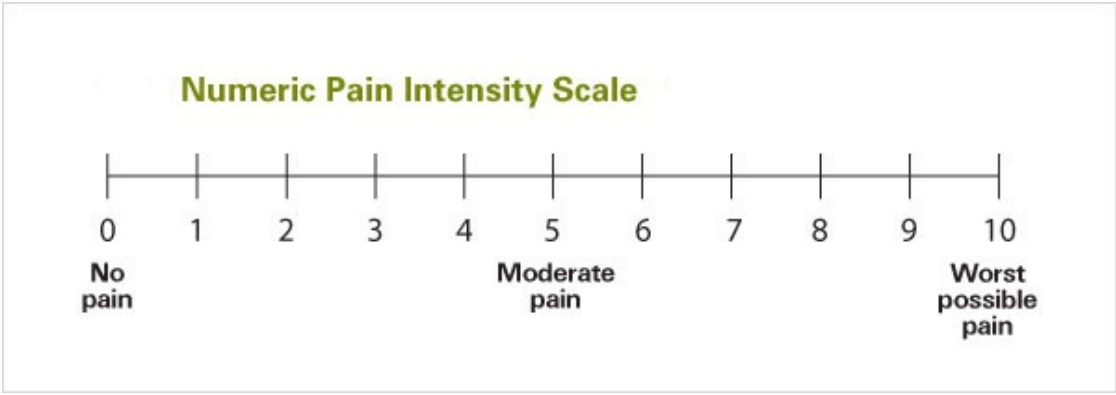
Visual analog scale enables us, to assess the grade of the intensity of pain. It is a simple, efficient, non-invasive method. It is a 10 cm long scale with the end points labelled as ‘no pain’ and ‘worst possible pain’. The patient makes a mark on the scale at a point parallel to the intensity of pain he or she presently feels. This method of pain assessing scale is not useful for children, visually impaired persons and in those with cognitive impairment.





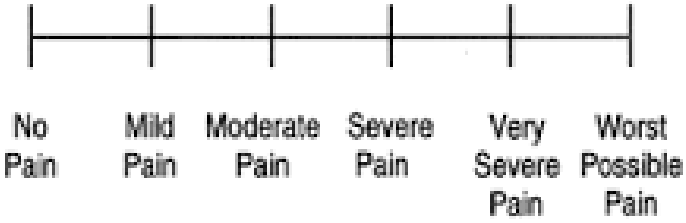
NUMERICAL RATING SCALE:

It closely resembles Visual analogue scale with a 10 cm line with left end marked as zero(indicating no pain) and right end as 10(indicating worst pain)with numbers marked in between from 1-9, having eleven points on scale. Patient will be asked to point out a number on the scale corresponding to the pain he or she feels that moment.



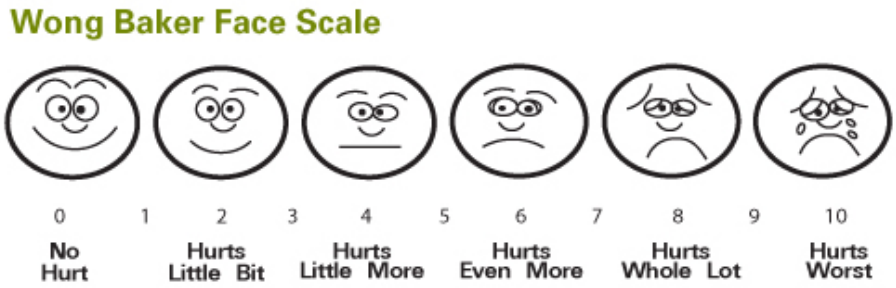
VERBAL RATING SCALE:

Here patients were asked to express their pain verbally as no pain, mild pain, moderate pain and severe pain. In this pain assessing method, Smallchange in pain intensity can be missed.



WONG BAKER FACES PAIN RATING SCALE:

It is for patients who cannot communicate and in children of 3- 7 years of age.



GABAPENTIN

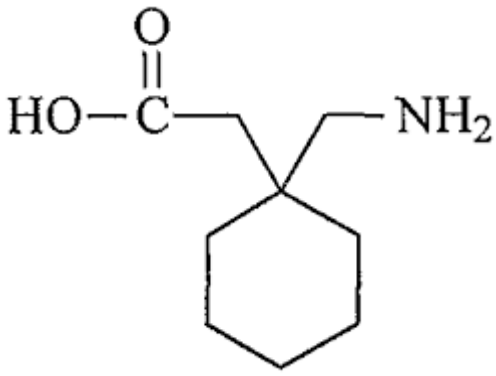
Gabapentin was introduced in early 1990s for the treatment of seizures.

Gabapentin belongs to second generation anticonvulsant drug, is an analog of GABA[12], where a GABA molecule is covalently bound to a lipophilic isobutene or cyclohexane ring. Later it was found to be efficient for the treatment of chronic pain conditions like diabetic neuropathy, post herpetic neuralgia, HIV related neuropathy, trigeminal neuralgia, inflammatory pain, malignant pain, and complex regional pain syndromes.

Also recent evidences are favouring perioperative administration and its efficacy in preoperative anxiolysis, attenuation of the hemodynamic response to laryngoscopy and intubation, and in prevention of chronic post-surgical pain, postoperative nausea and vomiting, and delirium.[53]

CHEMISTRY:

Gabapentin, an inhibitory neurotransmitter,1-(amino methyl)cyclohexane acetic acid, is a structural analogue of GABA.[53]



Molecular formula: C9H17NO2

Molecular weight: 171.24

Gabapentin is freely soluble in water, white to off-white crystalline solid, Highly charged at physiological PH existing as a zwitterion with a pKa1 of 3.7 and a pKa2 of 10.7. The log of the partition coefficient at PH 7.4 is –1.25.

For drug assay in urine and plasma, high performance liquid chromatography and gas chromatography are used.[53]

PHARMACOKINETICS:

All pharmacological actions are due to the activity of the parent compound, Gabapentin is not appreciably metabolised in humans.[54]

Oral bioavailability:

Gabapentin bioavailability is not dose dependant; i.e., as dose is increased, bioavailability decreases. Bioavailability of 300mg and 600 mg Gabapentin is 60% and 40% respectively[55]. Food has slight effect on the rate and extent of absorption of Gabapentin

Distribution:

Gabapentin is extensively distributed in human tissues and fluid after administration. Volume of distribution is 0.6- 0.81 / kg. It is not bound to plasma proteins. As it is highly ionised at physiological PH, concentration in adipose tissue is low. Gabapentin is highly lipid soluble, crosses blood brain barrier. Concentration in CSF is approximately 5-35% of those in plasma, whereas in brain tissue it is 80% of those in plasma. Peak plasma concentration is reached in 2-3 hrs after oral intake.

Metabolism:

Gabapentin is not significantly metabolized in humans. It does not induce hepatic microsomal enzymes.

Elimination:

Gabapentin is eliminated from the systemic circulation as unchanged drug in urine and unabsorbed drug is excreted in faces. Gabapentin elimination half-life is 5-7 hrs in normal renal function and is unaltered by dose or following multiple dosing. Gabapentin elimination rate constant, plasma clearance, and renal clearance are in direct proportion to creatinine clearance.

Gabapentin plasma clearance is reduced in elderly patients and in patients with impaired renal function. It can be cleared from plasma by hemodialysis.

Drug interactions:

Cimetidine, H2 receptor blockers decreases renal clearance when given currently.[35]Antacids when given concurrently, reduces the bioavailability of Gabapentin.[38]

Special situations:

Age: Renal clearance decreases with increasing age. Hence dose adjustment is required in patients who have age related decline in renal function.

Gender: There is no significant difference in gender. Pharmacokinetic parameters are similar in both sexes.

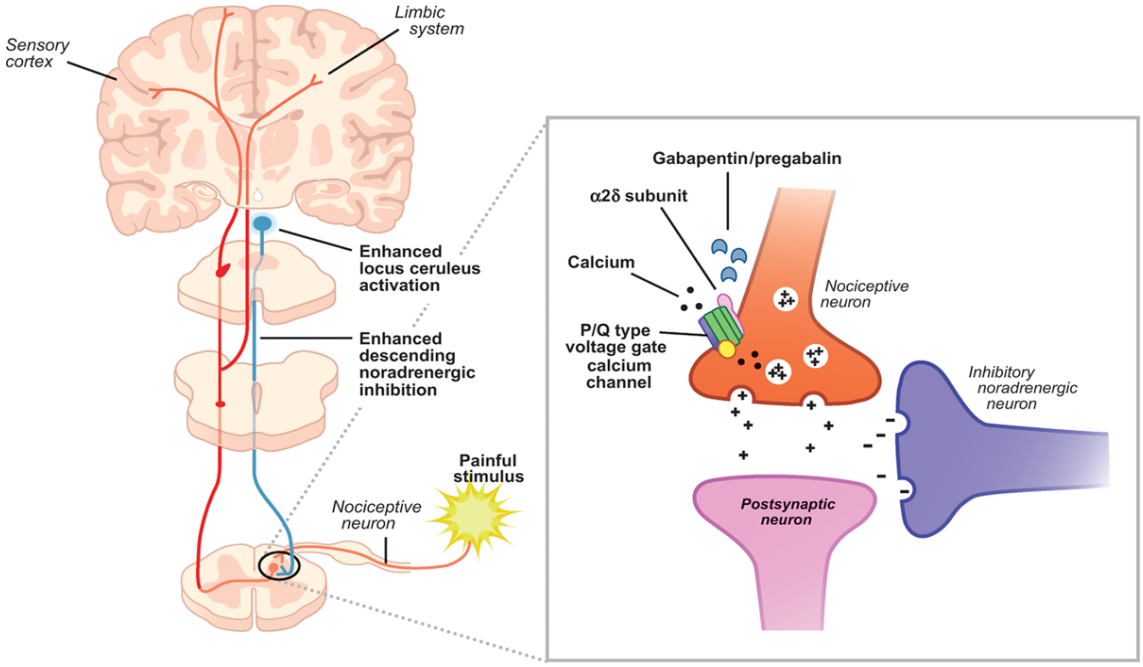
Renal insufficiency: The patients with reduced creatinine clearance are having increased half-life of Gabapentin. Hence dose adjustment is necessary.

Hemodialysis: The half-life of Gabapentin is reduced in patients on dialysis.

Hepatic diseases: Since Gabapentin is not metabolised in humans. No study was performed in patients with hepatic impairment.

Pregnancy and lactation: Gabapentin has been assigned to pregnancy category C. Fetotoxicity involving delayed ossification of several bones been revealed in animal studies. There is no controlled data in human studies, so it should be given when benefit outweighs risk. Gabapentin is secreted into milk, hence used only when benefit outweighs the risk.

ANTINOCICEPTIVE MECHANISM:



Gabapentin selectively binds to the $\alpha_2\delta$ subunit of voltage gated Calcium channels (found high in cerebral cortex, superficial dorsal horn, cerebellum, hippocampus),principally to post synaptic channels and inhibits calcium influx through these channels. Thereby inhibiting the evoked release of glutamate, aspartate, substance P, and calcitonin gene-related peptide (CGRP) from the primary afferent nerve fibres in pain pathway and hence a reduction in neuronal hyper excitability.

Also Gabapentin acts on spinal α_2 Adrenoreceptor to produce analgesia by activating the descending spinal nor-adrenergic system by releasing noradrenaline.[47, 48]

Despite intensive studies, exact mechanism of action of Gabapentin not known.

A number of mechanisms may be involved in the actions of Gabapentin.[4]

Despite its structural similarityto GABA,it does not act via mechanisms related to GABA[3] Possible proposed mechanism:

- Selective stimulation of the heterodimeric GABA B receptor which consist of GABA B_{1a} and GABA B_2 subunits.[3,29]
- Augmentation of the N-methyl-D-aspartate (NMDA) current at GABAergic interneurons.[14]
- Delaying a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor mediated transmission in the spinal cord.[40]
- Binding to the L-a-amino acid transporter;[11, 42] activating adenosine triphosphate sensitive Kβ (KATP) channels.[27]
- activating hyperpolarization-activated cation current (Ih) channels.[46]
- modulating Ca_2 β current by selectively binding to [3H]Gabapentin (a radio ligand), the $\alpha_2\delta$ subunit of voltage-dependent Ca_2 β channels(VGCCs).[46, 9]

Currently, VGCC is the most likely analgesic target of Gabapentin.

ERIOPERATIVE BENEFITS OF GABAPENTIN [53]

All perioperative applications are “off label” (the use of drugs outside the terms of their licence in clinical practice)

- in perioperative anxiolysis
- in post-operative analgesia
- in attenuating hemodynamic response to laryngoscopy and intubation
- In prevents chronic post-surgical pain, post-operative nausea, vomiting and delirium.

CLONIDINE

Clonidine, an imidazole derivative of α_2 agonist was originally introduced as vasoconstrictor and as topical nasal decongestant. It is a selective partial agonist for α_2 Adreno receptors.[17] It has variety of actions including antihypertensive effects as well as the ability to potentiate the effects of local anaesthetics. Clonidine can be administered orally, intravenously, intramuscularly, transdermally, epidurally, and intrathecally.[17]

PHYSIOCHEMICAL PROFILE

Clonidine hydrochloride is produced by chemical synthesis. It is an odourless, white crystalline powder having bitter taste.

Molecular weight : 266.6

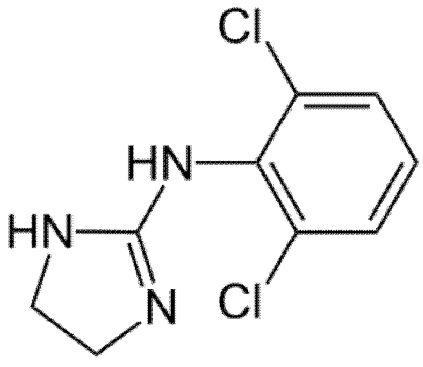
PKa1 : 8.3

Solubility in alcohol : 1 in 25

Solubility in water : 1 in 13

Octanol / water partial coefficient : 3.02

Structure: 2,6, dichloro N-2 imidazolinyieldene Benzenamine hydrochloride



PHARMACOLOGY:

Clonidine is a partial agonist at α adreno receptors both with in the central nervous system and in the periphery[17]. It has 300 times more affinity to α_2 than for α_1[17]. In CNS, α_2 receptors are located pre-synaptically (on neurons which release norepinephrine, epinephrine, serotonin and acetylcholine) and post synaptically (on noradrenergic neurons).

PHARMACOKINETICS:

Elimination half-life: 12-24 hrs

Volume of distribution: 2L/kg

Plasma protein binding: 20-40%

Pre-systemic metabolism: 0-25%

Oral Bioavailability: 95%-100%

Clonidine is lipid soluble and it readily crosses blood brain barrier. The peak concentration is observed at 1-3 hours after oral use and the maximal hypotensive effect occurs in this duration. Clonidine has varying bioavailability as an oral, transdermal, and parenteral preparation and can be used in epidural, intravenous, oral and rectal routes.

METABOLISM

Clonidine is approximately 50% metabolised in liver to inactive metabolites. Hydroxylated metabolites undergo secondary conjugation with sulphate or glucuronide and excreted renally. Metabolites do not have significant biological activity. Elimination half-life of Clonidine is about 9-12 hrs.Clearance may be

reduced in the renal dysfunction.Clonidine crosses the placental barrier, but doesnot reach concentration sufficient to harm the foetus.

DOSAGE:

Oral – bolus of 4-5 mcg/kg

Intramuscular – bolus of 2mcg/kg

Intravenous - bolus of 4-5 mcg/kg, continuous infusion at 2mcg/kg/hr

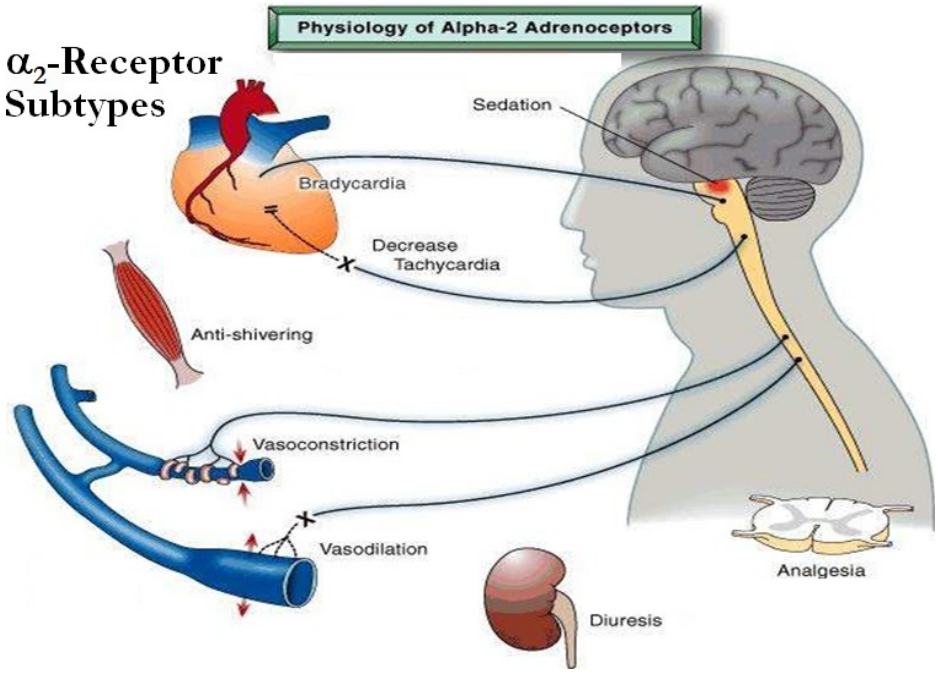
Epidural – bolus of 75-40mcg/kg, continuous infusion of 12.5-70 mcg/hour

Intrathecal- bolus of 30-225 mcg/kg, continuous infusion of 8-400mcg/day

Peripheral nerve block- 1-2 mcg/kg

Intra articular - 2mcg/kg

EFFECTS ON ORGAN SYSTEM:



1. CARDIOVASCULAR SYSTEM:

Administration of oral or intravenous Clonidine will cause a dose dependant drop in blood pressure and heart rate in both supine and standing position, orthostatic hypotension being more prominent. If Clonidine is administered rapidly as intravenous, there will be a brief pressor phase lasting less than 5 minutes with a MAP of less than 10 mmHg followed by hypotensive effect, which is more rapid with intravenous administration. The time of maximum effect (1.5-2 hrs) is similar in both routes. The degree of bradycardia is more marked after rapid intravenous administration. The extent of hypotension is also dose related and may extend for 24 hrs after single dose of 150-300 mcg. The magnitude of hypotensive effect is more with hypertensive individuals than normotensive subjects.

Stimulation of α_2 adrenergic neurons in the medullary vasomotor centre and in the nucleus tractussolitarius, leads to inhibition of sympathetic outflow leading to bradycardia and hypotension.

It decreases blood pressure from reduction of cardiac output due to reduced heart rate and relaxation of capacitance vessels as well as decrease in peripheral vascular resistance[30]. The pressor response with high dose of Clonidine is mediated by stimulation of α_1 or $\alpha_2$adrenorecptors on vascular smooth muscles leading to peripheral vasoconstriction.[30]

Anti arrhythmic properties: Clonidine is capable of preventing adrenaline induced arrhythmias during halothane anaesthesia.

2. RESPIRATORY SYSTEM:

Respiratory depression is seen with massive doses. However clinically we never use such higher doses. Clonidine is less potent than opioids. Nebulised Clonidine attenuates bronchoconstriction in asthmatic patients.

3. CENTRAL NERVOUS SYSTEM:

- Sedation is facilitated by central α_2 receptors in locus ceruleus[30]
- Provides anxiolysis equivalent to Benzodiazepines.
- Analgesia – Clonidine and Opioids act via different receptor mechanisms. Clonidine acts via α_2 adrenoreceptors in the superficial layers of dorsal horn, on the sensory afferents and on descending noradrenergic fibres from the brain stem, thereby inhibiting the spinal transmission of noxious stimulus by reducing the release of substance P.

4. RENAL SYTEM:

Clonidine produces diuresis, possibly by:

1. Inhibiting ADH and renin release.
2. Increasing atrial natriuretric peptide release.
3. Increasing GFR.
4. Antagonising the renal tubular action of ADH.

5. ENDOCRINE SYSTEM:

$\alpha_2$agonist prevents sympathetic adrenal flow and release of neurotransmitter at the neuroeffector junction.

Endocrine effects of α2 adrenoreceptor stimulation are

- Increase in secretion of TSH & GH
- Decrease in secretion of ACTH & ADH
- Inhibition of glucose stimulated insulin release by directly acting on islets cells of langerhan, but will not result in severe hyperglycemiaas this effect is transient in a clinical setting.

6. GASTRO INTESTINAL SYSTEM:

Stimulation of peripheral presynaptic α_2 adreno-receptors, on post ganglionic noradrenergic or cholinergic neurons reduces salivary flow, inhibits bowel motility and release of gastric secretion.

7. HEMATOLOGICAL SYSTEM:

Clonidine produces platelet aggregation. But, this effect is largely compensated by the decrease in circulating catecholamines.

OTHER USES :[17, 43, 30]

- Antihypertensive agent
- Anaesthesia: As premedication, prolonging the action of local anaesthetic in neuraxial blockade, in decreasing post-anaesthetic shivering.
- Treatment of Opioid and alcohol withdrawl
- Glaucoma(apraClonidine and brimonidine)
- Prophylaxis of migraine
- For Menopausal symptoms
- Diarrhoea in diabetic neuropathy
- Chronic pain syndromes
- Protection against perioperative Myocardial ischemia
- In Tics
- For Nicotine withdrawl
- In Psychiatric disorders
- Provocative test of GH secretion, for investigating short stature.
- In the diagnosis of Pheochromocytoma

CONTRAINDICATIONS:

- Clonidine hypersensitivity
- Atrioventricular node disease (sick sinus syndrome) or bradyarrhythmia
- In patients with cardiac pacemakers.
- Severe cardiovascular disease
- In hemodynamically unstable patients

DRUG INTERACTIONS :[17]

- Clonidine interacts with Tricyclic antidepressants which possess α_2 antagonist action, thereby blocking the antihypertensive effect of Clonidine

ADVERSE EFFECTS:[17]

- Common:
  - Sedation, dry mouth, Bradycardia, which responds to atropine, Hypotension, Constipation, Contact dermatitis.
- Less common:
  - Postural hypotension, fluid retention (oedema, weight gain), Sleep Disturbances (insomnia, hallucinations), confusion, headache, impotence, Parotid pain, Depression.
- Uncommon:
  - rash, pruritis, angioedema, hepatitis, gynacomastia, Raynaud's phenomenon, thinning of hair, urinary retention, agitation.
- Withdrawl syndrome:

Rapid rise in blood pressure, with headache, flushing, sweating, insomnia,agitation, tremor, nausea and vomiting presenting, 18-72 hours after last dose of Clonidine. It can be prevented bytapering Clonidine over days to weeks. It can be controlled by inhibiting peripheral sympathetic activity with $\alpha_2$adrenoreceptor antagonists or by reintroducing Clonidine treatment.

BENEFITS OF CLONIDINE AS PREMEDICATION:

- Blunts reflex tachycardia with Orotracheal intubation
- Reduces vasomotor liability
- Plasma catecholamines are decreased
- Clonidine decreases the MAC value to 50% ofinhalational agents and decreases analgesic requirements of opioids.

REVIEW OF LITERATURE

There has been numerous studies on search for newer drugs for attenuating intubation response and for decreasing postoperative pain.

1. In 1986, Ghignone M et al, [10] studied the effects of oral Clonidine on depths of fentanyl anaesthesia & on cardiovascular response to laryngoscopy & intubation in 24 patients undergoing aorto coronary bypass surgery & concluded that oral Clonidine reduced the fentanyl requirement and prevented the haemodynamic response to intubation.
2. In 1993, Laurito et al [23] found that Clonidine blunted the haemodynamic response with respect to HR, SBP and DBP to 15 sec laryngoscopy but not to 45 sec laryngoscopy when compared with the corresponding control group.2
3. In 1998, Batra YK et al, [2] studied the attenuation of heart rate and blood pressure response to laryngoscopy and intubation by Clonidine in forty health patients. Heart rate and blood pressure were significantly lower in the Clonidine treated group immediately after intubation.
4. In 2000, Matot et al [24] study shows that, in patients undergoing laryngoscopic or bronchoscopic procedures under general anaesthesia, premedication with oral Clonidine (4-4.5 µg/kg) attenuates haemodynamic responses. In this study, premedication with Clonidine 0.2mg administered 90 minutes prior to surgery significantly reduced HR, DAP, SAP, MAP changes for 10 min after endotracheal intubation.
5. In 2004, Turan et al,[50] performed a study by giving preoperative Gabapentin and its role in reducing pain score and requirement of tramadol in abdominal hysterectomy.The patients were monitored and found that VAS score and

total tramadol consumption were found to be lower in patients who received Gabapentin.

6. In 2004 Chandra Kant Pandey, MD ShioPriye, et al, [32] in 459 ASA PS I and II patients were randomly assigned to receive 300mg Gabapentin, 100 mg Tramadol, and placebo in a double blinded manner 2 hours before laparoscopic cholecystectomy under general anaesthesia.They concluded less fentanyl was consumed in the Gabapentin group than in the tramadol and placebo group. Sedation, nausea, retching/ vomiting was the commonest side effects in the Gabapentin whereas respiratory depression was the commonest in tramadol group and vertigo in placebo group.
7. In 2005, C.K. Pandey et al, [31] conducted a study about postoperative pain and requirement of analgesics in patients undergoing lumbar discectomy by giving pre-operative Gabapentin 300 mg. It was found that pain score and fentanyl requirement was less in patients who received Gabapentin pre-operatively.
8. In 2006, Turan b, Kumaralingalou et al [51], investigated the effects of Gabapentin on acute postoperative pain and morphine consumption in patients undergoing spinal surgery. Their study showed that pre-operative oral Gabapentin decreased pain scores in the early post-operative period and post-operative morphine consumption in patients who underwent spinal surgery while decreasing some morphine associated side effects.
9. In 2006, Hussain Al- mujadi et al [1]conducted a study by administering Gabapentin 1200 mg and placebo capsules,2 hours prior to thyroidectomy surgery for postoperative pain,morphine requirement and its side effect. They

concluded that patient who received Gabapentin had decreased pain scores and morphine requirement with insignificant side effects.

10. In 2006, A.Fassoulaki et al, [7] studied the effect of Gabapentin alone on post laryngoscopy and tracheal intubation pressor response with forty six patients who underwent abdominal hysterectomy or benign diseases. They monitored systolic and diastolic blood pressure, heart rate before and after anaesthetic and 0,1,3,5,10 minutes after tracheal intubation. Conclusion of the study was that pressor responses could be attenuated but not the tachycardia associated with laryngoscopy and tracheal intubation.
11. In 2006, Memis et al, [26] studied the effect of Gabapentin on cardiovascular responses to laryngoscopy and tracheal intubation in normotensive patients. In this study 90 ASA I patients.They concluded that oral administration of Gabapentin 800 mg but not 400 mg given 1 hour before operation blunted the arterial pressure and HR increase in the first 10 min after endotracheal intubation.
12. In 2007 O Kiskira et al,[21] conducted a study by using Gabapentin (800 mg) pre-operatively, for patients undergoing orthopaedic procedures and assessed the post-op pain intensity and requirement of analgesics.It was found that post-operative pain score and morphine requirement was lesser in these patients during first 24 hours.
13. In 2009 Indira Kumari et al [16], have studied the changes in SBP, DBP, MAP and HR following laryngoscopy and tracheal intubation after administering Gabapentin 900 mg, 2 hours before induction. Significant rise in SBP,DBP, and MAP were observed following laryngoscopy and tracheal intubation in placebo group as compared to Gabapentin group. No significant change in

heart rate was documented in both the groups. They concluded that both Gabapentin and Clonidinehad effective role in blunting hemodynamic responses after laryngoscopy, more with Gabapentin.2

14. In 2009, Seyed Mojtaba Marashi et al [39] , conducted a study to compare the efficacy of Gabapentin and Clonidineas premedication in modifying the hyperdynamic response following laryngoscopy and tracheal intubation, with 75 ASA I and II patients of both sexes, of age 18-45 yrs.
15. In 2010, Nagwa M. Doha et al, [28] investigated the efficacy of Gabapentin (1200 mg) regarding the requirement of analgesic intra-operatively and post-operatively in mastectomy surgeries. Intraoperative need of anaesthetic and analgesic requirement was lower in those who received Gabapentin as well as post-operative VAS score and analgesic requirement was also reduced with increased incidence of dizziness.
16. In 2011, Kamran Montazeri et al, [18] also compared the efficacy of oral Gabapentin and Clonidine aspremedicaion for controlling the pressor response to laryngoscopy and tracheal intubation, where 96 patients were studied. In this study they concluded, that premedication with oral Gabapentin 800 mg or Clonidine 0.3 mg, blunted the hyperdynamic response after laryngoscopy and intubation.
17. In 2011, Usha Bafna et al, [52] did a comparison study of different doses of Gabapentin to attenuate the pressor response to laryngoscopy and tracheal intubation in normotensive patients. In this study 90 ASA I and II patients aged 20-60 years were taken. They concluded that Gabapentin 1000mg given 1 hour before operation significantly attenuated the hemodynamic response in normotensive patients.

18. In 2014, Suresh K Singhal et al, [45] compared Oral Gabapentin and Clonidine as premedication for obtunding hemodynamic response to laryngoscopy and tracheal intubation. In this study 100 patients,50 of each group of ASA I and II patients were given oral Gabapentin 900mg and Clonidine 0.2 mg prior to induction and concluded that oral Clonidine compared with oral Gabapentin obtunded the pressor response. Also Clonidine was superior with sedation and anxiolysis than Gabapentin.

METHODS AND MATERIALS

After obtaining approval from the Institutional Ethical Committee and written informed consent from all the patients, the study was conducted in RGGGH, in Surgical Gastroenterologist operation theatre in patients scheduled for elective laparoscopic cholecystectomy under general anaesthesia.

Study design:

Randomised, clinical study, Group A (Gabapentin) will receive 900mg Tab. Gabapentin, Group B (Clonidine) receiving 0.2 mg Tab. Clonidine and Group C (Placebo) receiving Tab. Vitamin C .

INCLUSION CRITERIA:

Age : 18 – 60 years.

Weight : BMI < 30 Kg/m2

American Society of anaesthesiologist physical status I & II patients.

Surgery : Elective

Mallampatti scores : I & II

Patients who have given valid informed consent.

EXCLUSION CRITERIA:

Patients who are not satisfying inclusion criteria.

Patients posted for emergency surgery

Patients with difficult airway

Lack of written informed consent

H/O seizures and any neurological deficit

Renal or liver disease.

Recent consumption of analgesics in past 24 hours

Known allergy or sensitivity to the drugs.

Ongoing therapy with sustained release opioids.

Cases which have been converted from laparoscopic to open surgery.

Sample Size Calculation

Sample size was determined based on **the study of "**Effect of oral Clonidine premedication on perioperative haemodynamic response and postoperative analgesic requirement for patients undergoing laparoscopic cholecystectomy**"** authored by Shivinder Singh et al Published in Indian J Anaesth 2011;55:26-30.

In this study Remarkably less patients were given a single dose of meperidine during the first 24 hours postoperatively in the Clonidine group (72% v 32%, $P < 0.05$). and showing a significant difference in scoring by 40%.

Description:

- The confidence level is estimated at 95% with a z value of 1.96
- The confidence interval or margin of error is estimated at +/-12
- Assuming that the sample will have the specified attribute p% =40 and q%=60

  $n = p\% \times q\% \times [z/e\%]^2$

  $n= 40 \times 60 \times [1.96/12]^2$

  $n= 64.02$

Therefore 64 is the minimum sample size required for the study

In our study we have taken 75 as the sample size

- n=25 in Group Gabapentin
- n=25 in Group Clonidine
- n=25 in Group Placebo

MATERIALS

Monitors- ECG, NIBP, SPO2, EtCo2.

Drugs: Injection Midazolam, Injection Glycopyrrolate, Inj Fentanyl, Inj.Thiopentone Sodium, Inj. atracurium, Inj. Neostigmine, sevoflurane, emergency drugs, Normal Saline and Ringer Lactate.

Airway devices : Mactintosh Laryngoscope, Guedel's Oral Airway, Gum elastic bougie.

Boyles anaesthesia machine

Patients satisfying inclusion criteria were randomly allocated by closed envelope method into 3 groups: Group A (Gabapentin), Group B (Clonidine), Group C (Placebo). Patients were examined the evening before surgery. They were described about the study methods, the visual analogue scale chart and along with information sheet. All were orally premedicated with alprazolam 0.5mg at 9.00 pm, the day before surgery.

In the preoperative room, A good intravenous access was secured and baseline parameters were noted which includes heart rate (HR), systolic blood pressure(SBP), Diastolic blood pressure(DBP), Mean arterial pressure(MAP) and pulse-oximetry (SPO2). Patients in group A received Tab Gabapentin 900 mg orally , Group B patients will received Tab. Clonidine 0.2mg and Group C patients will received Tab. Vitamin C with sips of water 90 minutes prior to induction. Vital parameters were recorded 3 minutes before induction. After premedication with Inj.Glycopyrrolate 0.2 mg IV, Inj.Midazolam 1mg IV, Inj.Fentanyl 2 mcg/ kg IV was given and preoxygenation done. Anaesthesia was induced with Inj.Thiopentone sodium 5 mg/ kg IV or dose adequate to abolish eye lash reflex, and was followed by a muscle relaxant Inj. Atracurium 0.5 mg/ kg IV to facilitate laryngoscopy and intubation. Patients were ventilated by mask for atleast 3 minutes using 100% oxygen with sevoflurane 1%. Laryngoscopy was performed with a Macintosh laryngoscope and trachea was intubated with appropriate sized endotracheal tube by a trained anaesthesiologist. The period of laryngoscopy and intubation was less than 15 seconds for all patients. Heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, pulse-oximetry was monitored and recorded at the time of intubation and at 1,3,5,10 minutes after intubation. Maintenance of anaesthesia was carried out

using nitrous oxide and oxygen in the ratio of 2:1, sevoflurane 1-2% using controlled ventilation.

Patient was observed for complications like hypotension, hypertension, arrhythmias, hypoxemia, and bronchospasm and treated as required. Hypotension is defined as fall in SBP/DBP by 30% from baseline and was treated with a bolus of intravenous fluid or Inj. Ephedrine 3mg. Bradycardia defined as decrease in heart rate to less than 60 min and it was managed with Inj. Atropine 0.6 mg iv and Tachycardia is defined as heart rate more than 100/min. Hypertension is when systolic blood pressure is more than 30% from baseline. This response was treated by increasing the concentration of inhalational anaesthetic agent Sevoflurane and supplemental bolus of fentanyl 0.5 mcg/kg.

At the end of the surgery, residual neuromuscular blockade was reversed with Inj. Neostigmine 0.05 mg/kg and Inj. Glycopyrrolate 0.01 mg/kg intravenously. Immediate post-extubation, vital parameters, sedation score, anxiety scores were recorded. Patient was shifted to PACU and was monitored for vital parameters. VAS score and vital parameters were assessed for 1, 2, 4, 6, 8 hours postoperatively.

Patients were given Inj. Fentanyl 0.5mcg/kg intravenously when the VAS score was >3, which was repeated until the pain subsided. Total analgesic requirement in postoperative period was recorded. VAS scoring, Ramsay Sedation Scoring,Anxiety Scoring and side effects like nausea, vomiting and dizziness were recorded.

RAMSEY SEDATION SCORE:

1. Anxious, agitated, or restless
2. Cooperative, oriented and tranquil

3. Responds to command
4. Asleep but has a brisk risk to light glabellar tap or loud auditory stimulus
5. Asleep but has a sluggish response to light glabellar tap or loud auditory stimulus
6. Asleep, no response

ANXIETY SCORE [33]

0 - patient quiet and comfortable

1 - patient uneasy

2 - patient worried or anxious

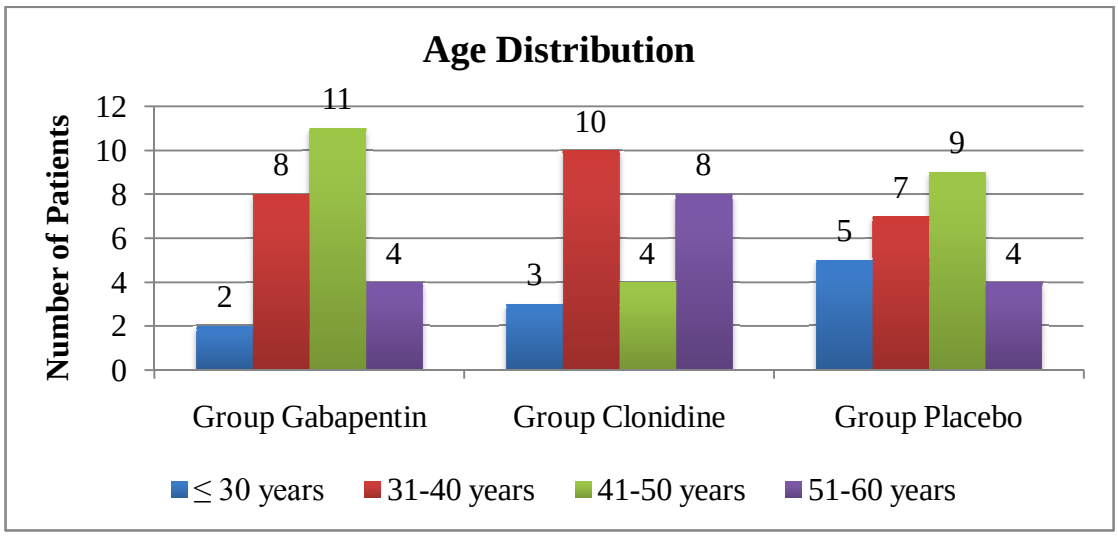
3 - patient very worried or very upset

4 - patient frightened or terrified.

STATISTICAL METHODS

Descriptive statistics was done for all data and suitable statistical tests of comparison were done. These included the mean and standard deviation (SD) for quantitative variables, and category frequency counts for qualitative variables. Next, inferential statistical analysis was undertaken. Continuous variables were analysed with the unpaired t-test and categorical variables were analysed with the Chi-Square Test with Yates correction. Alpha for significance for all inferences was set at $P<0.05$. All tests of Hypotheses, wherever applicable, were two-tailed. The data was analysed using SPSS version 16 and Microsoft Excel 2007.

Age

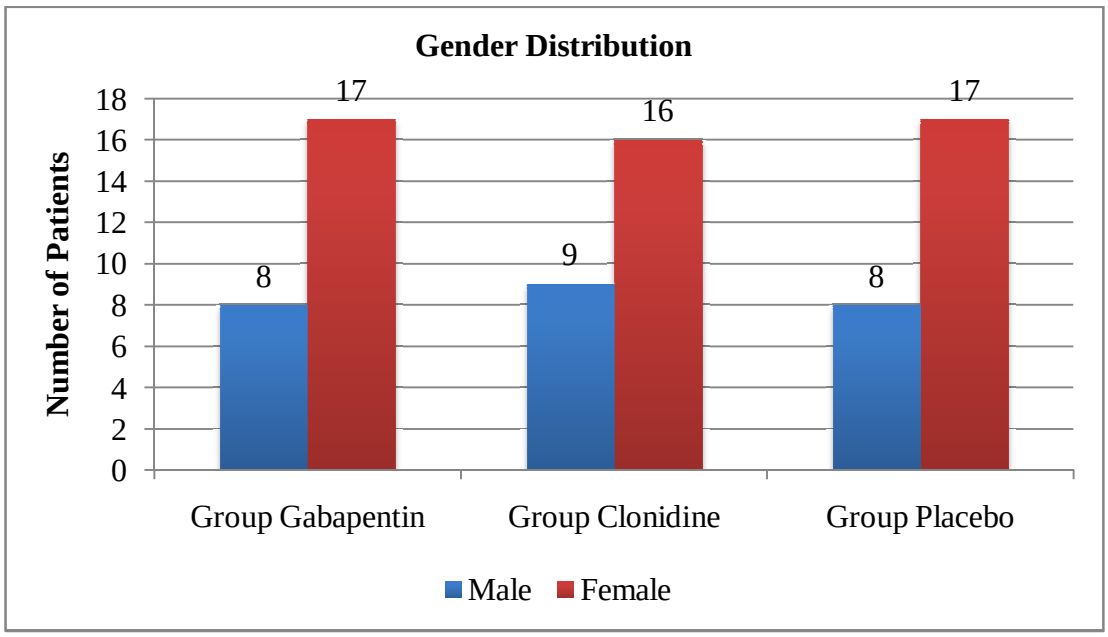


Age Distribution	Group Gabapentin	%	Group Clonidine	%	Group Placebo	%
≤ 30 years	2	8.00	3	12.00	5	20.00
31-40 years	8	32.00	10	40.00	7	28.00
41-50 years	11	44.00	4	16.00	9	36.00
51-60 years	4	16.00	8	32.00	4	16.00
Total	25	100	25	100	25	100

Age Distribution	Group Gabapentin	Group Clonidine	Group Placebo
N	25	25	25
Mean	44.28	42.44	40.56
SD	9.68	11.49	10.29
P value Unpaired t Test	Group Gabapentin vs Group Clonidine		0.5433
	Group Gabapentin vs Group Placebo		0.1943
	Group Clonidine vs Group Placebo		0.5451

Majority of the group Gabapentin patients belonged to the 41-50 years age class interval (n=11, 44%) with a mean age of 44.28 years. In the group Clonidine patients, majority belonged to the 31-40 years age class interval (n=10, 40%) with a mean age of 42.44 years. Similarly in the group Placebo patients, majority belonged to the 41-50 years age class interval (n=9, 36%) with a mean age of 42.44 years. The association between the intervention groups and age distribution is considered to be not statistically significant since $p > 0.05$ as per 2 tail unpaired t test.

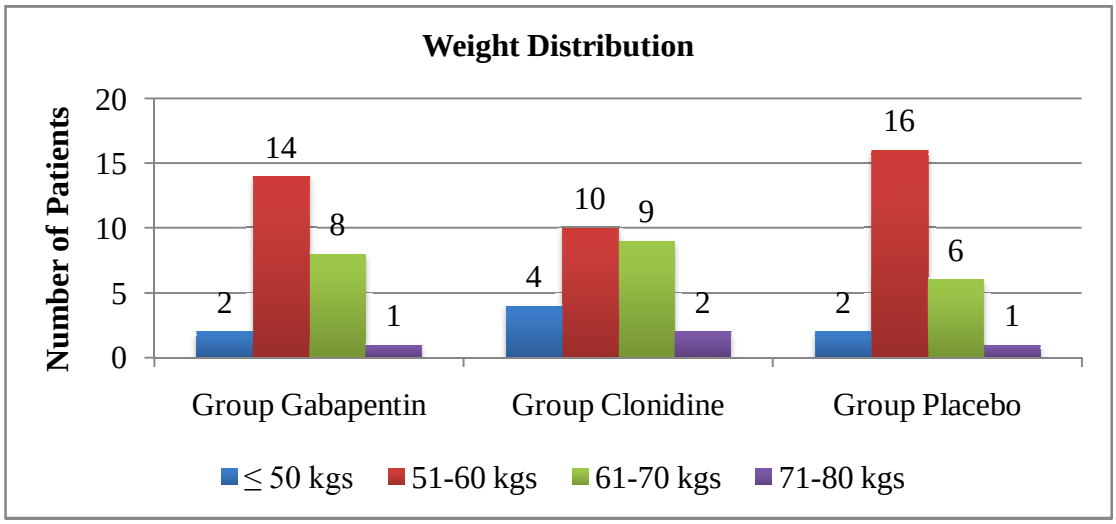
Gender



Gender Distribution	Group Gabapentin	%	Group Clonidine	%	Group Placebo	%
Male	8	32.00	9	36.00	8	32.00
Female	17	68.00	16	64.00	17	68.00
Total	25	100	25	100	25	100
P value Chi Squared Test		Group Gabapentin vs Group Clonidine			0.7653	
		Group Gabapentin vs Group Placebo			>0.9999	
		Group Clonidine vs Group Placebo			0.7653	

Majority of the group Gabapentin patients belonged to female gender (n=17, 68%). In the group Clonidine patients, majority belonged to female gender (n=16, 64%). Similarly in the group Placebo patients, majority belonged to female gender (n=17, 68%). The association between the intervention groups and gender distribution is considered to be not statistically significant since $p > 0.05$ as per chi squared test.

Weight

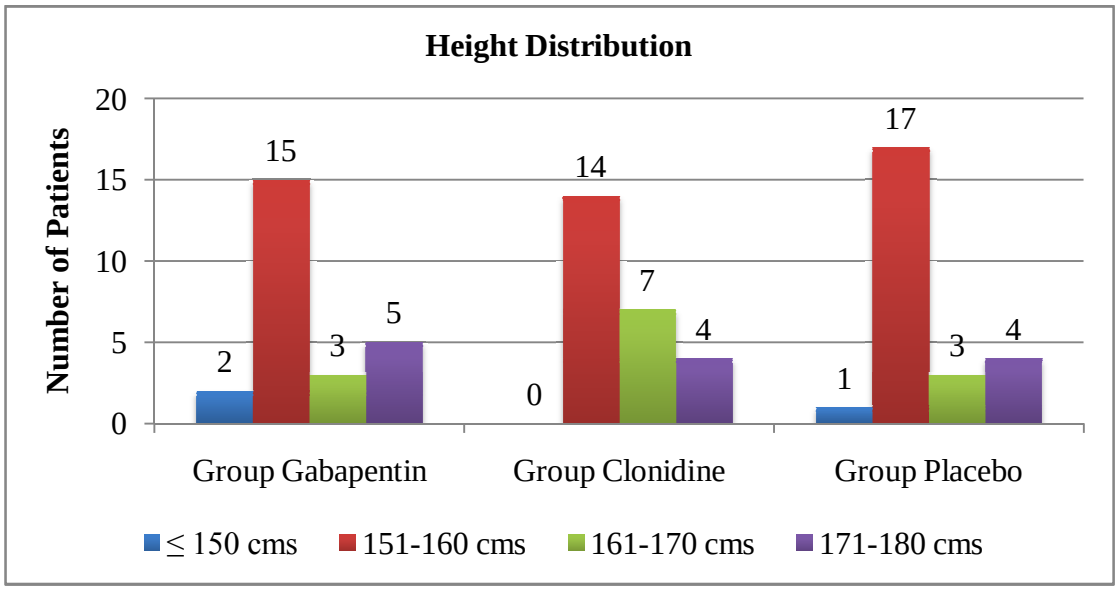


Weight Distribution	Group Gabapentin	%	Group Clonidine	%	Group Placebo	%
≤ 50 kgs	2	8.00	4	16.00	2	8.00
51-60 kgs	14	56.00	10	40.00	16	64.00
61-70 kgs	8	32.00	9	36.00	6	24.00
71-80 kgs	1	4.00	2	8.00	1	4.00
Total	25	100	25	100	25	100

Weight Distribution	Group Gabapentin	Group Clonidine	Group Placebo
N	25	25	25
Mean	59.00	59.76	57.20
SD	6.95	7.47	5.71
P value Unpaired t Test	Group Gabapentin vs Group Clonidine		0.7112
	Group Gabapentin vs Group Placebo		0.3220
	Group Clonidine vs Group Placebo		0.1803

Majority of the group Gabapentin patients belonged to the 51-60 kgs weight class interval (n=14, 56%) with a mean weight of 59.00 kgs. In the group Clonidine patients, majority belonged to the 51-60 kgs weight class interval (n=10, 40%) with a mean weight of 59.76 kgs. Similarly in the group Placebo patients, majority belonged to the 51-60 kgs weight class interval (n=16, 64%) with a mean weight of 57.20 kgs. The association between the intervention groups and weight distribution is considered to be not statistically significant since $p > 0.05$ as per 2 tail unpaired t test.

Height

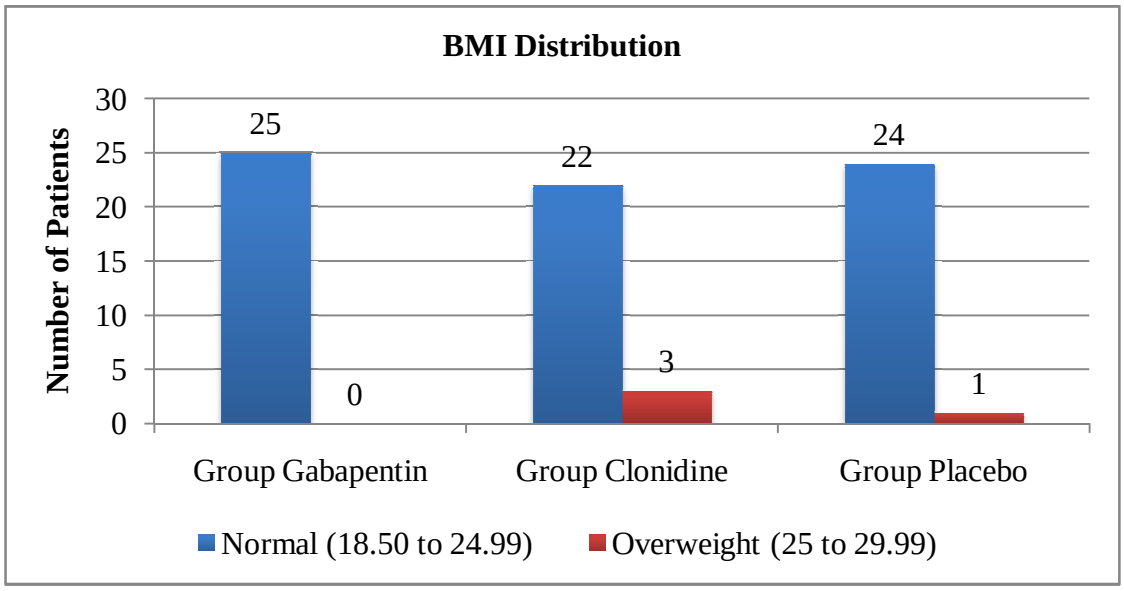


Height Distribution	Group Gabapentin	%	Group Clonidine	%	Group Placebo	%
≤ 150 cms	2	8.00	0	0.00	1	4.00
151-160 cms	15	60.00	14	56.00	17	68.00
161-170 cms	3	12.00	7	28.00	3	12.00
171-180 cms	5	20.00	4	16.00	4	16.00
Total	25	100	25	100	25	100

Height Distribution	Group Gabapentin	Group Clonidine	Group Placebo
N	25	25	25
Mean	159.20	160.36	160.16
SD	8.51	7.42	8.03
P value Unpaired t Test	Group Gabapentin vs Group Clonidine		0.6098
	Group Gabapentin vs Group Placebo		0.6835
	Group Clonidine vs Group Placebo		0.9275

Majority of the group Gabapentin patients belonged to the 151-160 cms height class interval (n=15, 60%) with a mean height of 159.20 cms. In the group Clonidine patients, majority belonged to the 151-160 cms height class interval (n=14, 56%) with a mean height of 160.36 cms. Similarly in the group Placebo patients, majority belonged to the 151-160 cms height class interval (n=17, 68%) with a mean height of 160.16 cms. The association between the intervention groups and height distribution is considered to be not statistically significant since $p > 0.05$ as per 2 tail unpaired t test.

BMI

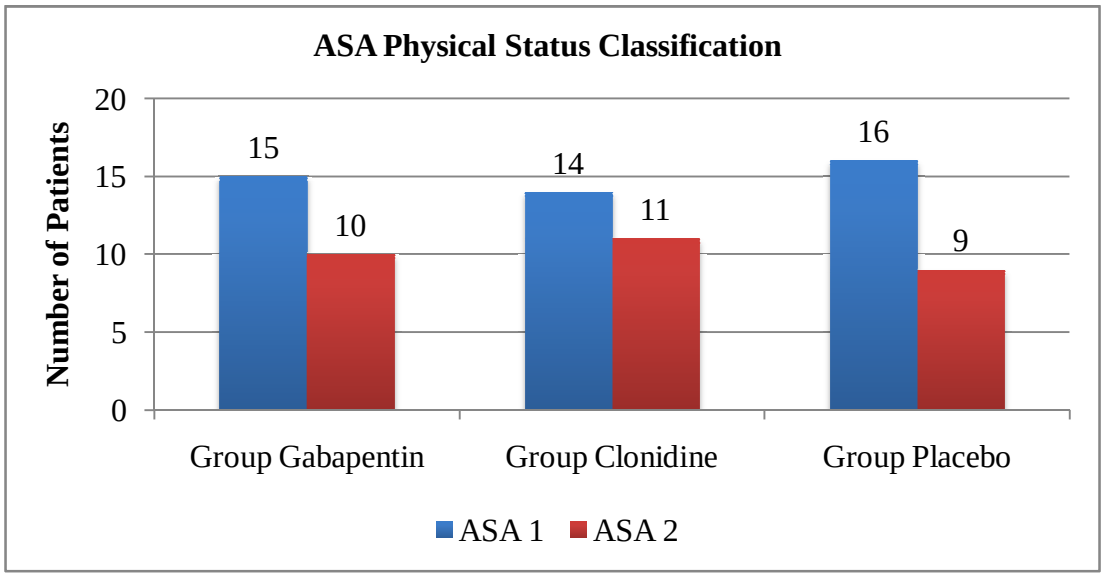


BMI Distribution	Group Gabapentin	%	Group Clonidine	%	Group Placebo	%
Underweight (≤ 18.49)	0	0.00	0	0.00	0	0.00
Normal (18.50 to24.99)	25	100.00	22	88.00	24	96.00
Overweight (25 to 29.99)	0	0.00	3	12.00	1	4.00
Obese	0	0.00	0	0.00	0	0.00
Total	25	100	25	100	25	100

BMI Distribution	Group Gabapentin	Group Clonidine	Group Placebo
N	25	25	25
Mean	23.17	23.18	22.39
SD	1.21	1.88	1.60
P value Unpaired t Test	Group Gabapentin vs Group Clonidine		0.9794
	Group Gabapentin vs Group Placebo		0.0563
	Group Clonidine vs Group Placebo		0.1128

Majority of the group Gabapentin patients belonged to the Normal BMI class interval (n=25, 100%) with a mean BMI of 23.17. In the group Clonidine patients, majority belonged to the Normal BMI class interval (n=22, 88%) with a mean BMI of 23.16. Similarly in the group Placebo patients, majority belonged to the Normal BMI class interval (n=24, 96%) with a mean BMI of 22.39. The association between the intervention groups and BMI distribution is considered to be not statistically significant since $p > 0.05$ as per 2 tail unpaired t test.

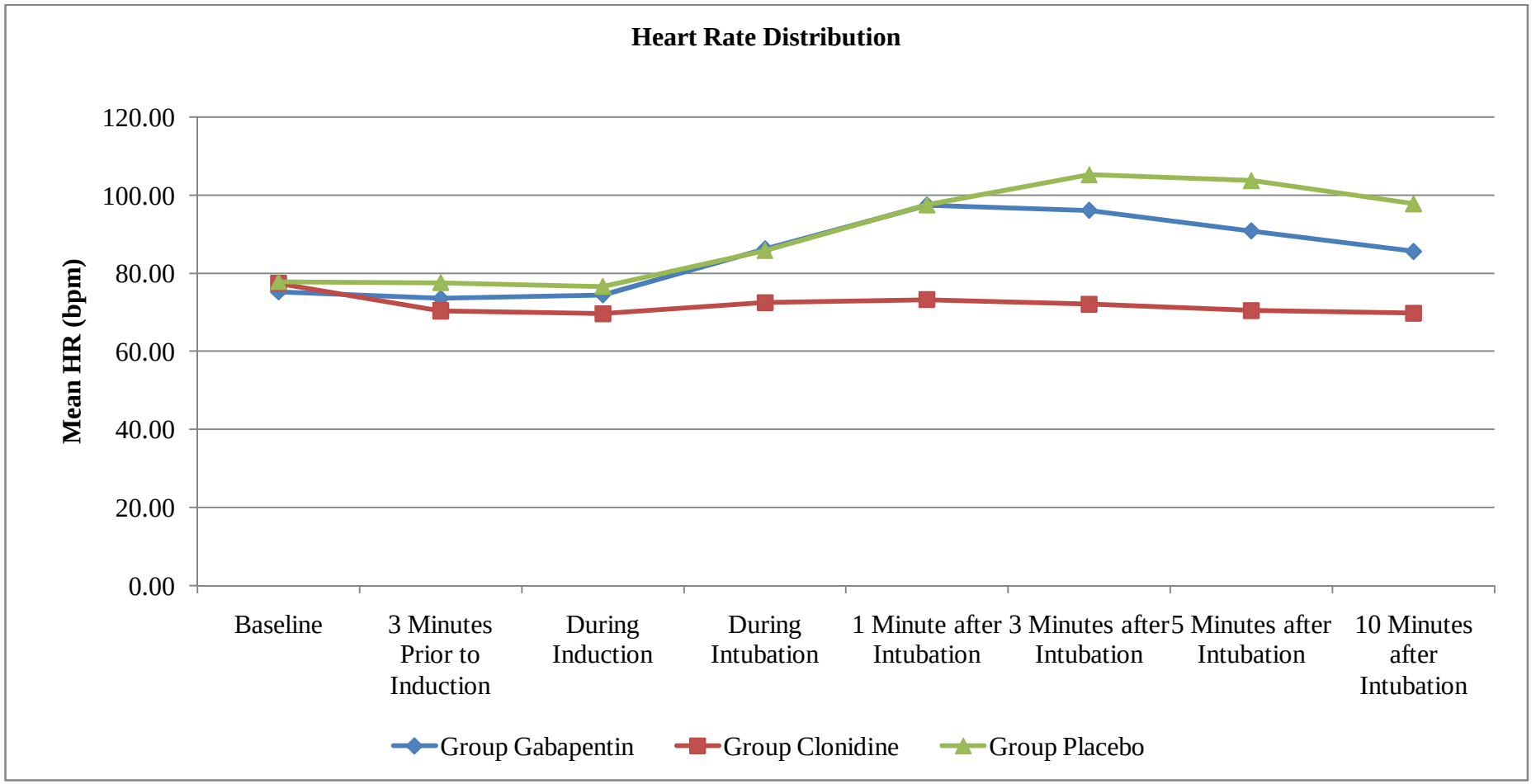
ASA



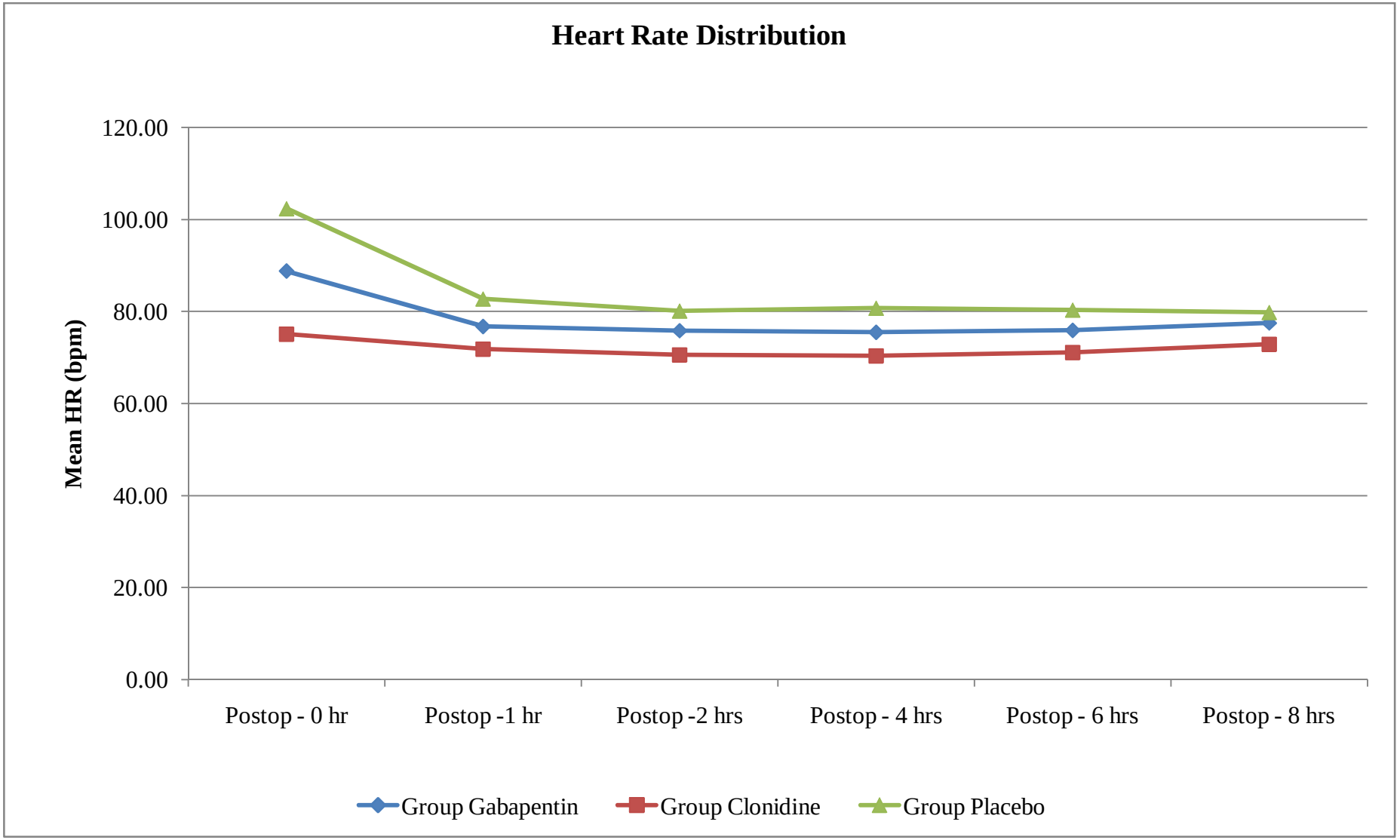
ASA Physical Status Classification	Group Gabapentin	%	Group Clonidine	%	Group Placebo	%
ASA 1	15	60.00	14	56.00	16	64.00
ASA 2	10	40.00	11	44.00	9	36.00
Total	25	100	25	100	25	100
P value Chi Squared Test		Group Gabapentin vs Group Clonidine			0.7745	
		Group Gabapentin vs Group Placebo			0.7708	
		Group Clonidine vs Group Placebo			0.5637	

Majority of the group Gabapentin patients belonged to ASA Physical Status Classification 1 (n=15, 60%). In the group Clonidine patients, majority belonged to ASA Physical Status Classification 1 (n=14, 56%). Similarly in the group Placebo patients, majority belonged to ASA Physical Status Classification 1 (n=16, 64%). The association between the intervention groups and ASA Physical Status Classificationis considered to be not statistically significant since $p > 0.05$ as per chi squared test.

Heart Rate


Heart Rate Distribution
Mean HR (bpm)
120.00
100.00
80.00
60.00
40.00
20.00
0.00
Baseline
3 Minutes Prior to Induction
During Induction
During Intubation
1 Minute after Intubation
3 Minutes after Intubation
5 Minutes after Intubation
10 Minutes after Intubation
Group Gabapentin
Group Clonidine
Group Placebo

Heart Rate Distribution		Baseline	3 Minutes Prior to Induction	During Induction	During Intubation	1 Minute after Intubation	3 Minutes after Intubation	5 Minutes after Intubation	10 Minutes after Intubation
Group Gabapentin	N	25	25	25	25	25	25	25	25
	Mean	75.28	73.64	74.52	86.28	97.48	96.16	90.88	85.64
	SD	9.13	4.20	4.85	8.81	11.11	11.08	10.06	8.04
Group Clonidine	N	25	25	25	25	25	25	25	25
	Mean	77.44	70.40	69.68	72.52	73.28	72.12	70.48	69.80
	SD	8.60	5.91	4.69	7.19	5.26	4.56	5.82	5.18
Group Placebo	N	25	25	25	25	25	25	25	25
	Mean	77.88	77.64	76.64	85.80	97.52	105.24	103.80	97.84
	SD	9.72	12.76	11.14	6.84	7.60	7.24	8.44	9.59
P value Unpaired t Test	Group Gabapentin vs Group Clonidine	0.3936	0.0269	0.0010	0.0000	0.0000	0.0000	0.0000	0.0000
	Group Gabapentin vs Group Placebo	0.3345	0.0472	0.0393	0.0006	0.0182	0.0014	0.0000	0.0000
	Group Clonidine vs Group Placebo	0.8661	0.0141	0.0073	0.0000	0.0000	0.0000	0.0000	0.0000


Heart Rate Distribution
Mean HR (bpm)
120.00
100.00
80.00
60.00
40.00
20.00
0.00
Postop - 0 hr
Postop -1 hr
Postop -2 hrs
Postop - 4 hrs
Postop - 6 hrs
Postop - 8 hrs
Group Gabapentin
Group Clonidine
Group Placebo

Heart Rate Distribution		Post-op 0 hr	Post-op 1st hr	Post-op 2nd hr	Post-op 4th hr	Post-op 6th hr	Post-op 8th hr
Group Gabapentin	N	25	25	25	25	25	25
	Mean	88.76	76.76	75.84	75.52	75.92	77.52
	SD	6.49	5.86	5.34	4.47	4.83	4.00
Group Clonidine	N	25	25	25	25	25	25
	Mean	75.08	71.84	70.60	70.36	71.12	72.84
	SD	6.40	6.05	7.39	6.14	5.34	5.25
Group Placebo	N	25	25	25	25	25	25
	Mean	102.36	82.76	80.16	80.76	80.36	79.84
	SD	9.08	8.56	7.96	6.13	5.98	5.44
P value Unpaired t Test	Group Gabapentin vs Group Clonidine	0.0000	0.0053	0.0062	0.0015	0.0017	0.0009
	Group Gabapentin vs Group Placebo	0.0000	0.0060	0.0296	0.0012	0.0059	0.0930
	Group Clonidine vs Group Placebo	0.0000	0.0000	0.0001	0.0000	0.0000	0.0000

By conventional criteria the association between the intervention groups and heart rate status among study subjects is considered to be statistically significant since $p < 0.05$.

Results

In patients belonging to group Gabapentin, the mean heart rate is 82.69 bpm. In group Clonidine the mean heart rate is 71.55 bpm. Similarly in group placebo the mean heart rate is 88.52 bpm.

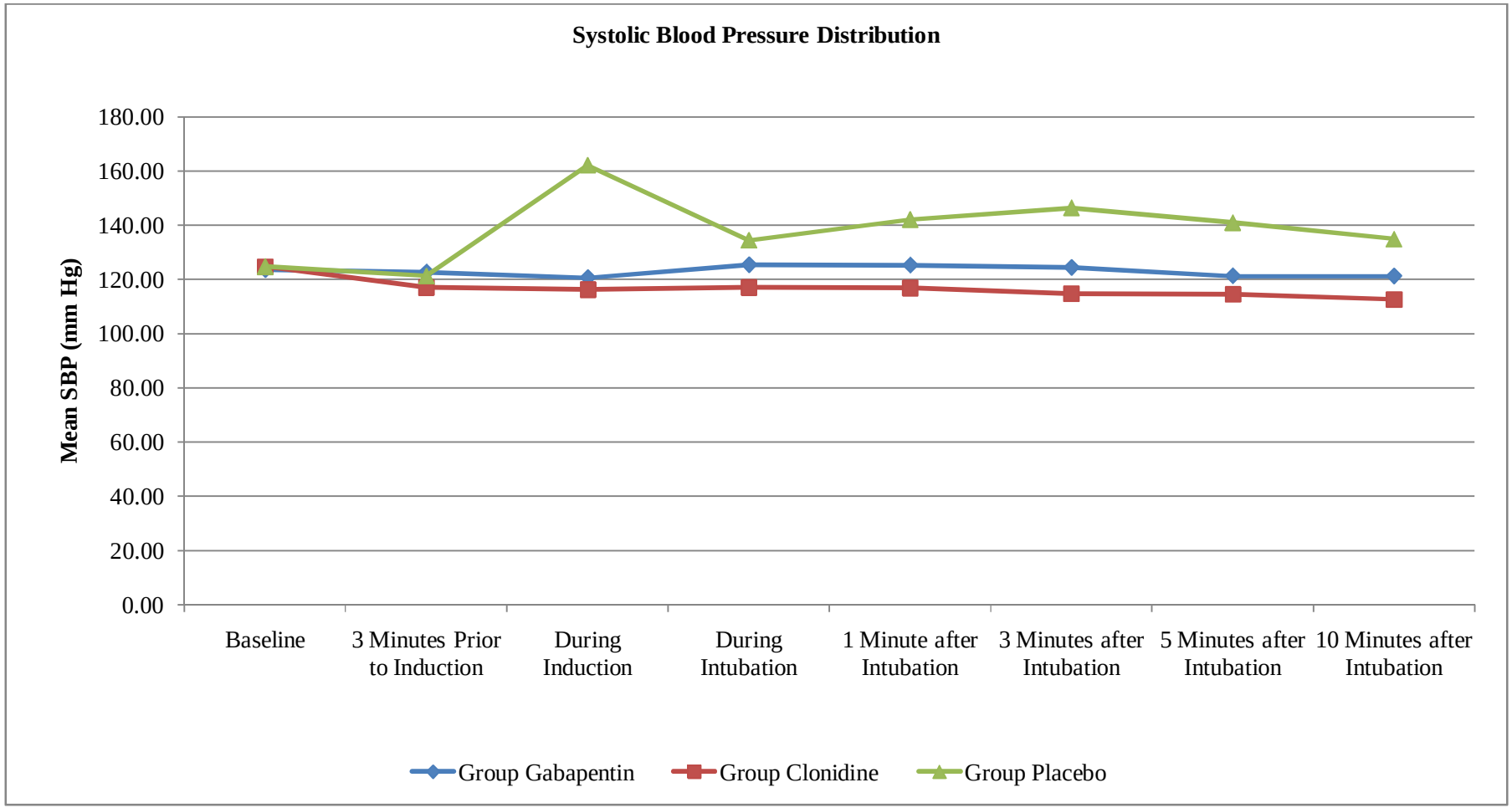
The increased the mean heart rate measurement in group Gabapentin compared to the group Clonidine is statistically significant as the p value is 0.0033 as per unpaired t-test indicating a difference among study groups.The mean heart rate measurement was meaningfully more in group Gabapentin compared to group Clonidine by 1.16 times with a mean difference of 11.14 bpm.

The decreased the mean heart rate measurement in group Gabapentin compared to the group placebo is statistically significant as the p value is 0.0197 as per unpaired t- test indicating a difference among study groups.The mean heart rate measurement was meaningfully less in group Gabapentin compared to group placebo by 7% with a mean difference of 5.83 bpm.

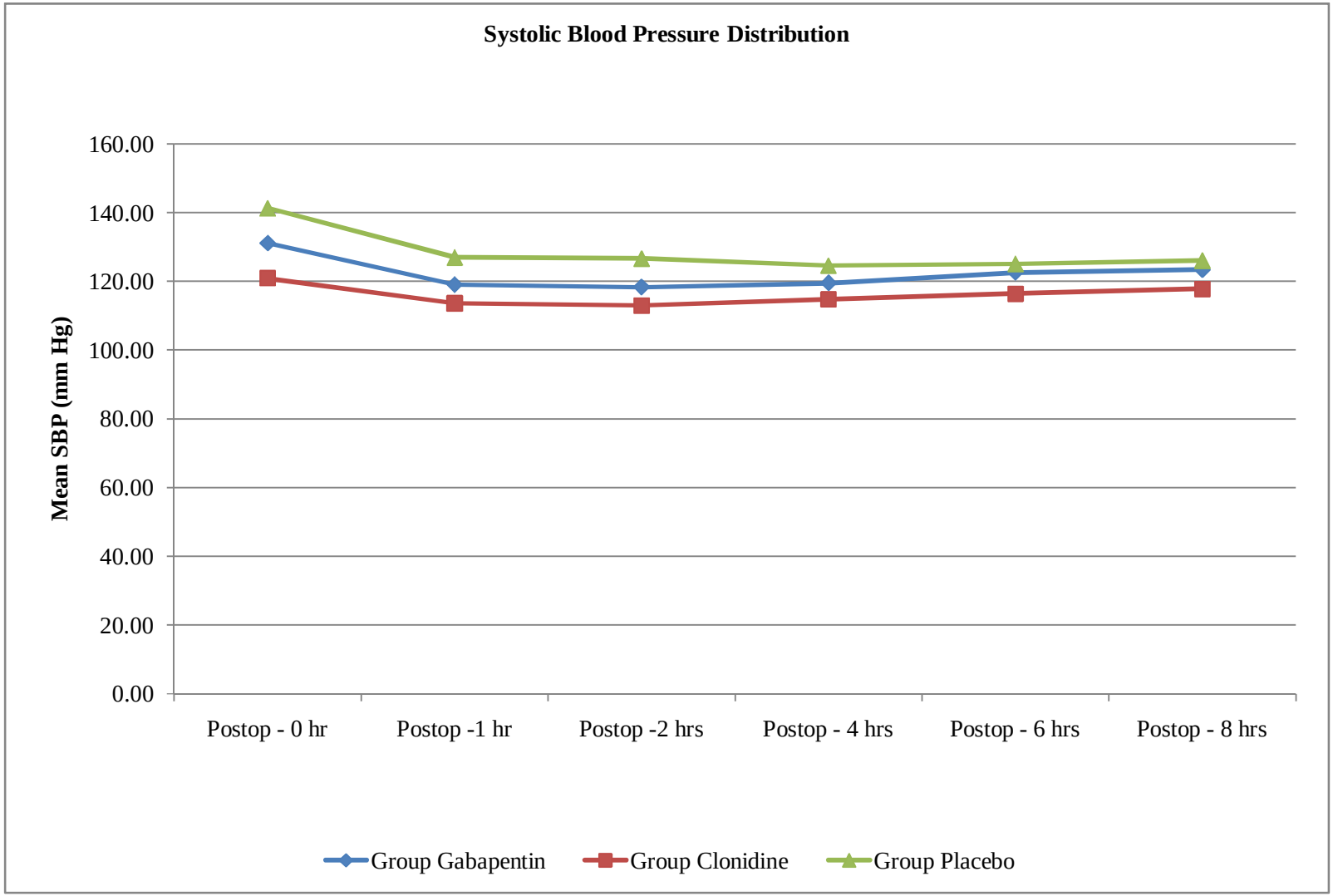
The decreased the mean heart rate measurement in group Clonidine compared to the group placebo is statistically significant as the p value is 0.0017 as per unpaired t- test indicating a difference among study groups.The mean heart rate measurement was meaningfully less in group Clonidine compared to group placebo by 19% with a mean difference of 16.97 bpm.

This difference is true and significant and has not occurred by chance.

SBP


Systolic Blood Pressure Distribution
Mean SBP (mm Hg)
180.00
160.00
140.00
120.00
100.00
80.00
60.00
40.00
20.00
0.00
Baseline
3 Minutes Prior to Induction
During Induction
During Intubation
1 Minute after Intubation
3 Minutes after Intubation
5 Minutes after Intubation
10 Minutes after Intubation
Group Gabapentin
Group Clonidine
Group Placebo

Systolic blood pressure Distribution		Baseline	3 Minutes Prior to Induction	During Induction	During Intubation	1 Minute after Intubation	3 Minutes after Intubation	5 Minutes after Intubation	10 Minutes after Intubation
Group Gabapentin	N	25	25	25	25	25	25	25	25
	Mean	123.60	122.72	120.64	125.36	125.20	124.40	121.28	121.24
	SD	10.89	7.62	7.61	8.72	5.70	7.56	4.94	4.40
Group Clonidine	N	25	25	25	25	25	25	25	25
	Mean	124.72	117.00	116.32	117.04	116.88	114.68	114.56	112.60
	SD	10.68	7.83	6.23	7.95	6.32	6.57	6.57	5.01
Group Placebo	N	25	25	25	25	25	25	25	25
	Mean	124.72	121.24	162.08	134.40	142.04	146.36	140.88	134.84
	SD	10.33	9.66	10.21	6.96	8.00	6.22	5.81	5.75
P value Unpaired t Test	Group Gabapentin vs Group Clonidine	0.7151	0.0090	0.0399	0.0009	0.0000	0.0000	0.0002	0.0000
	Group Gabapentin vs Group Placebo	0.7108	0.0459	0.0324	0.0002	0.0000	0.0000	0.0000	0.0000
	Group Clonidine vs Group Placebo	1.0000	0.0402	0.0257	0.0000	0.0000	0.0000	0.0000	0.0000


Systolic Blood Pressure Distribution
Mean SBP (mm Hg)
160.00
140.00
120.00
100.00
80.00
60.00
40.00
20.00
0.00
Postop - 0 hr
Postop -1 hr
Postop -2 hrs
Postop - 4 hrs
Postop - 6 hrs
Postop - 8 hrs
Group Gabapentin
Group Clonidine
Group Placebo

Systolic blood pressure Distribution		Post-op 0 hr	Post-op 1 hr	Post-op 2 hr	Post-op 4 hr	Post-op 6 hr	Post-op 8 hr
Group Gabapentin	N	25	25	25	25	25	25
	Mean	131.12	119.04	118.36	119.56	122.60	123.40
	SD	7.25	2.95	4.64	4.47	4.45	4.34
Group Clonidine	N	25	25	25	25	25	25
	Mean	120.92	113.64	113.00	114.76	116.48	117.80
	SD	5.57	6.84	7.19	6.04	6.25	4.76
Group Placebo	N	25	25	25	25	25	25
	Mean	141.28	126.96	126.60	124.56	125.08	126.04
	SD	6.52	5.40	6.08	4.01	6.03	4.63
P value Unpaired t Test	Group Gabapentin vs Group Clonidine	0.0000	0.0010	0.0032	0.0026	0.0003	0.0001
	Group Gabapentin vs Group Placebo	0.0000	0.0000	0.0000	0.0001	0.1053	0.0430
	Group Clonidine vs Group Placebo	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

By conventional criteria the association between the intervention groups and systolic blood pressure status among study subjects is considered to be statistically significant since $p < 0.05$.

Results

In patients belonging to group Gabapentin, the mean systolic blood pressure is 122.69 mm Hg. In group Clonidine the mean systolic blood pressure is 115.82 mm Hg. Similarly in group placebo the mean systolic blood pressure is 134.80 mm Hg.

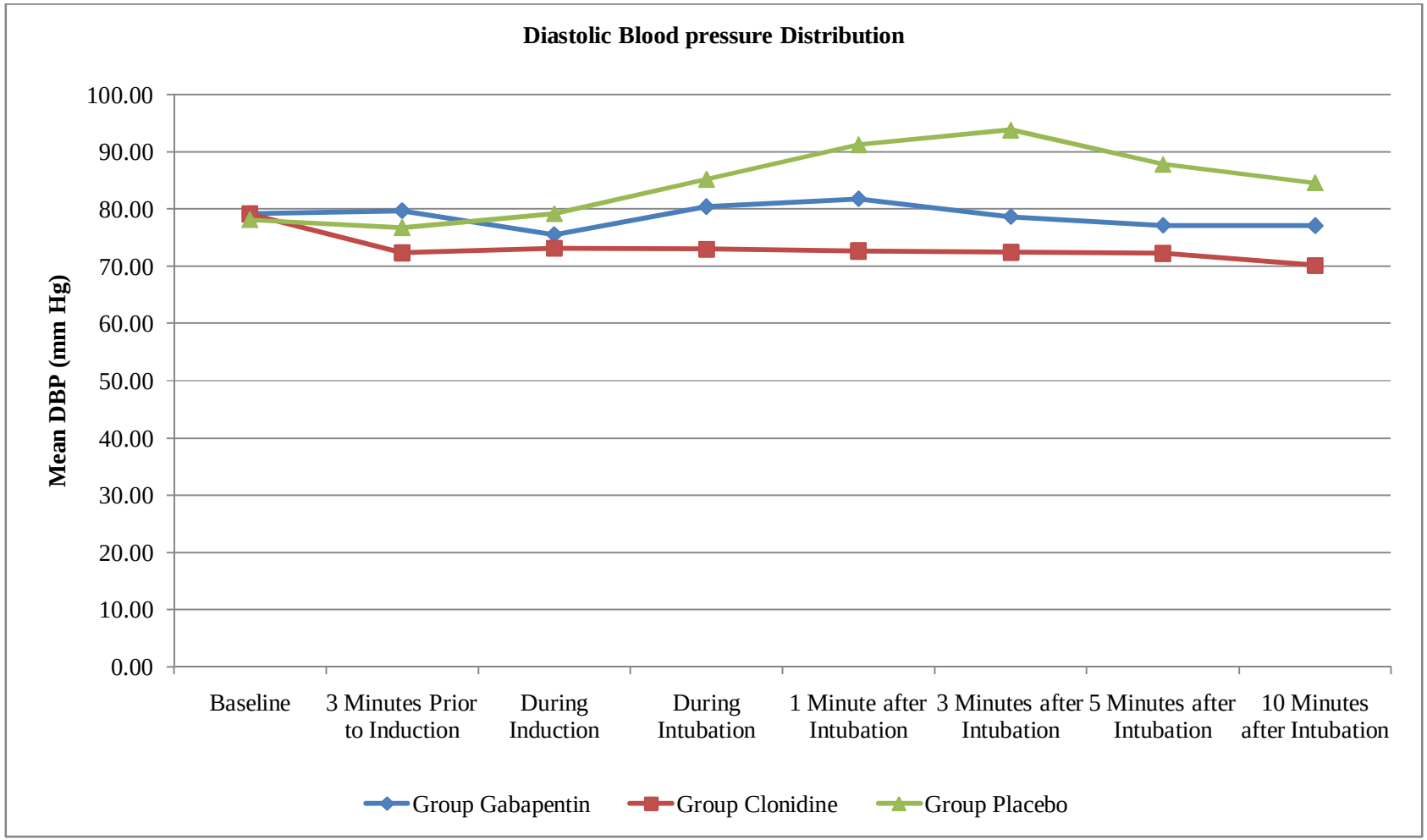
The increased the mean systolic blood pressure measurement in group Gabapentin compared to the group Clonidine is statistically significant as the p value is 0.0044 as per unpaired t- test indicating a true difference among study groups. The mean systolic blood pressure measurement was meaningfully more in group Gabapentin compared to group Clonidine by 1.06 times with a mean difference of 6.86 mm Hg.

The decreased the mean systolic blood pressure measurement in group Gabapentin compared to the group placebo is statistically significant as the p value is 0.0382 as per unpaired t- test indicating a true difference among study groups. The mean systolic blood pressure measurement was meaningfully less in group Gabapentin compared to group placebo by 9% with a mean difference of 12.11 mm Hg.

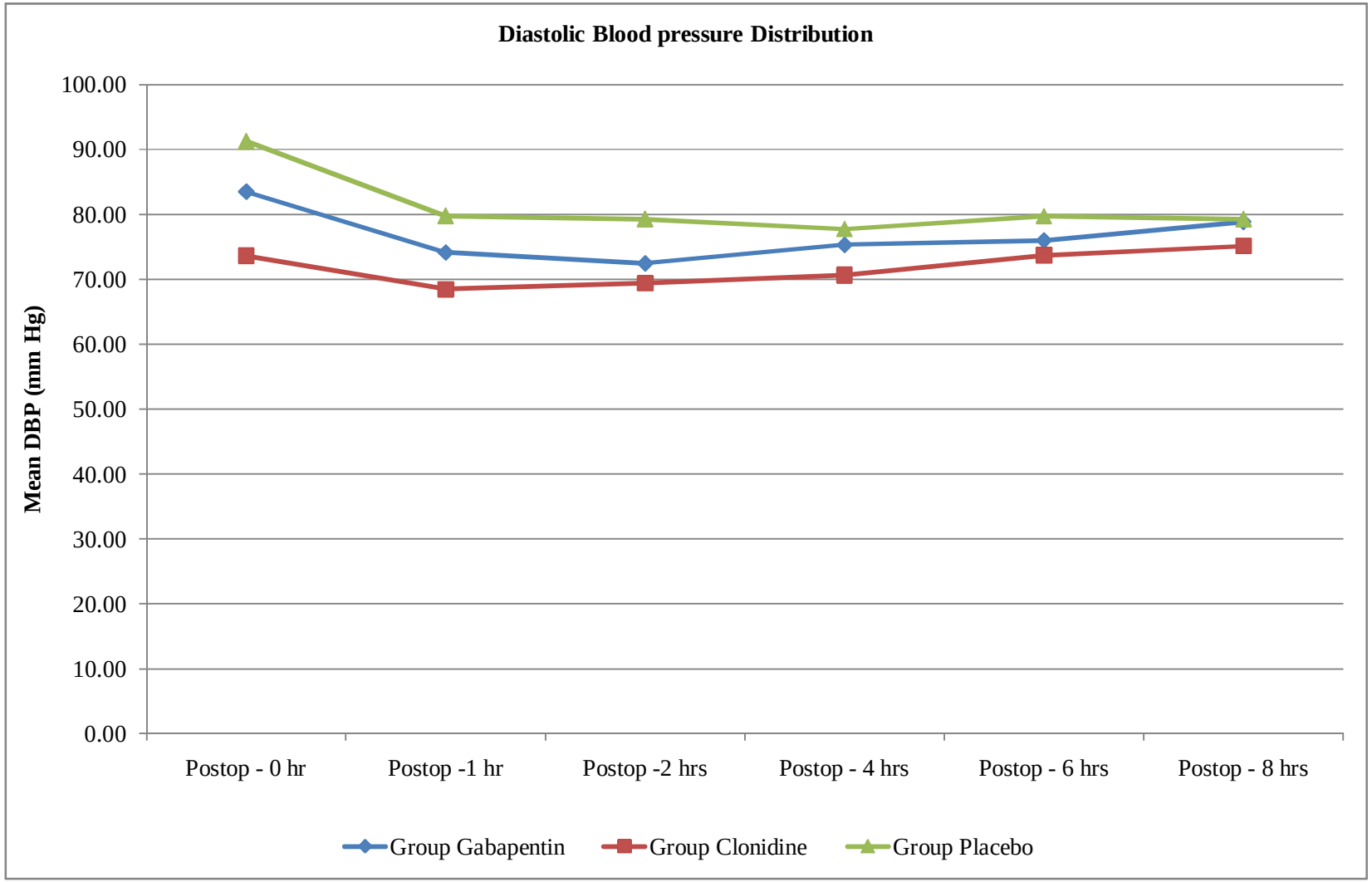
The decreased the mean systolic blood pressure measurement in group Clonidine compared to the group placebo is statistically significant as the p value is 0.0274 as per unpaired t- test indicating a true difference among study groups. The mean systolic blood pressure measurement was meaningfully less in group Clonidine compared to group placebo by 14% with a mean difference of 18.98 mm Hg.

This difference is true and significant and has not occurred by chance.

DBP


Diastolic Blood pressure Distribution
Mean DBP (mm Hg)
100.00
90.00
80.00
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
Baseline
3 Minutes Prior to Induction
During Induction
During Intubation
1 Minute after Intubation
3 Minutes after Intubation
5 Minutes after Intubation
10 Minutes after Intubation
Group Gabapentin
Group Clonidine
Group Placebo

Diastolic blood pressure Distribution		Baseline	3 Minutes Prior to Induction	During Induction	During Intubation	1 Minute after Intubation	3 Minutes after Intubation	5 Minutes after Intubation	10 Minutes after Intubation
Group Gabapentin	N	25	25	25	25	25	25	25	25
	Mean	79.20	79.68	75.56	80.40	81.80	78.68	77.16	77.08
	SD	8.07	5.11	6.33	6.89	4.48	4.99	4.17	5.14
Group Clonidine	N	25	25	25	25	25	25	25	25
	Mean	79.12	72.36	73.16	73.00	72.68	72.44	72.24	70.16
	SD	7.76	4.32	4.26	5.14	4.42	5.02	4.80	4.55
Group Placebo	N	25	25	25	25	25	25	25	25
	Mean	78.12	76.76	79.20	85.20	91.28	93.84	87.84	84.60
	SD	7.89	7.08	6.14	5.31	4.81	5.21	5.09	3.93
P value Unpaired t Test	Group Gabapentin vs Group Clonidine	0.9716	0.0000	0.0429	0.0001	0.0000	0.0001	0.0003	0.0000
	Group Gabapentin vs Group Placebo	0.6345	0.0119	0.0330	0.0083	0.0000	0.0000	0.0000	0.0000
	Group Clonidine vs Group Placebo	0.6536	0.0140	0.0002	0.0000	0.0000	0.0000	0.0000	0.0000


Diastolic Blood pressure Distribution
Mean DBP (mm Hg)
100.00
90.00
80.00
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
Postop - 0 hr
Postop -1 hr
Postop -2 hrs
Postop - 4 hrs
Postop - 6 hrs
Postop - 8 hrs
Group Gabapentin
Group Clonidine
Group Placebo

Diastolic blood pressure Distribution		Post-op 0 hr	Post-op 1st hr	Post-op 2nd hr	Post-op 4th hr	Post-op 6th r	Post-op 8th hr
Group Gabapentin	N	25	25	25	25	25	25
	Mean	83.48	74.16	72.48	75.32	76.00	78.84
	SD	6.29	4.62	3.47	4.32	4.11	3.95
Group Clonidine	N	25	25	25	25	25	25
	Mean	73.60	68.48	69.44	70.64	73.68	75.12
	SD	5.34	4.98	5.05	4.25	5.60	3.78
Group Placebo	N	25	25	25	25	25	25
	Mean	91.28	79.76	79.28	77.76	79.72	79.28
	SD	6.24	5.36	4.77	5.24	4.01	3.66
P value Unpaired t Test	Group Gabapentin vs Group Clonidine	0.0000	0.0001	0.0171	0.0007	0.1019	0.0007
	Group Gabapentin vs Group Placebo	0.0001	0.0003	0.0000	0.0288	0.0022	0.0048
	Group Clonidine vs Group Placebo	0.0000	0.0000	0.0000	0.0000	0.0001	0.0001

By conventional criteria the association between the intervention groups and diastolic blood pressure status among study subjects is considered to be statistically significant since $p < 0.05$.

Results

In patients belonging to group Gabapentin, the mean diastolic blood pressure is 77.74 mm Hg. In group Clonidine the mean diastolic blood pressure is 72.08 mm Hg. Similarly in group placebo the mean diastolic blood pressure is 83.52 mm Hg.

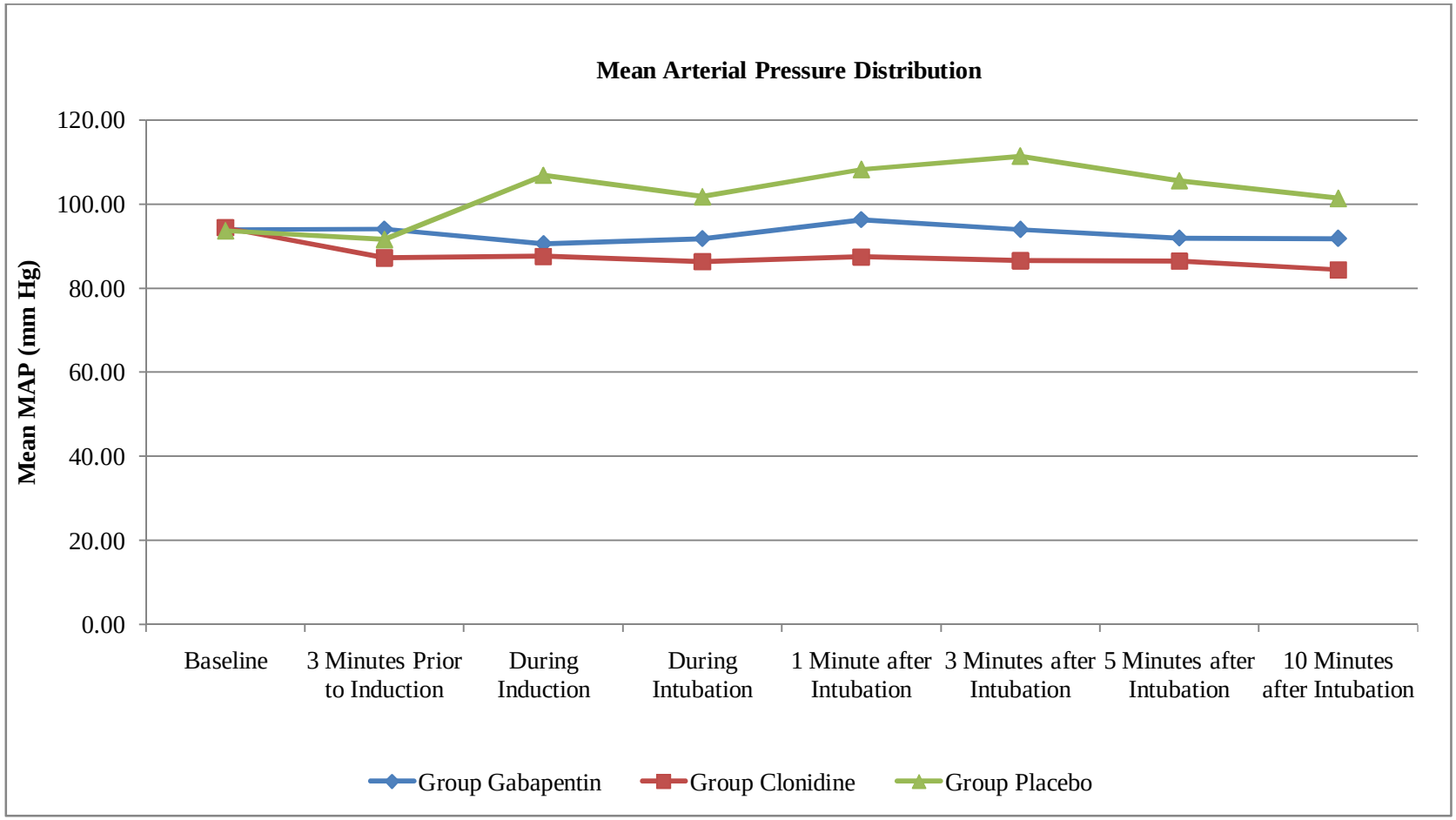
The increased the mean diastolic blood pressure measurement in group Gabapentin compared to the group Clonidine is statistically significant as the p value is 0.0203 as per unpaired t-test indicating a true difference among study groups.The mean diastolic blood pressure measurement was meaningfully more in group Gabapentin compared to group Clonidine by 1.08 times with a mean difference of 5.66 mm Hg.

The decreased the mean diastolic blood pressure measurement in group Gabapentin compared to the group placebo is statistically significant as the p value is 0.0415 as per unpaired t- test indicating a true difference among study groups. The mean diastolic blood pressure measurement was meaningfully less in group Gabapentin compared to group placebo by 7% with a mean difference of 5.78 mm Hg.

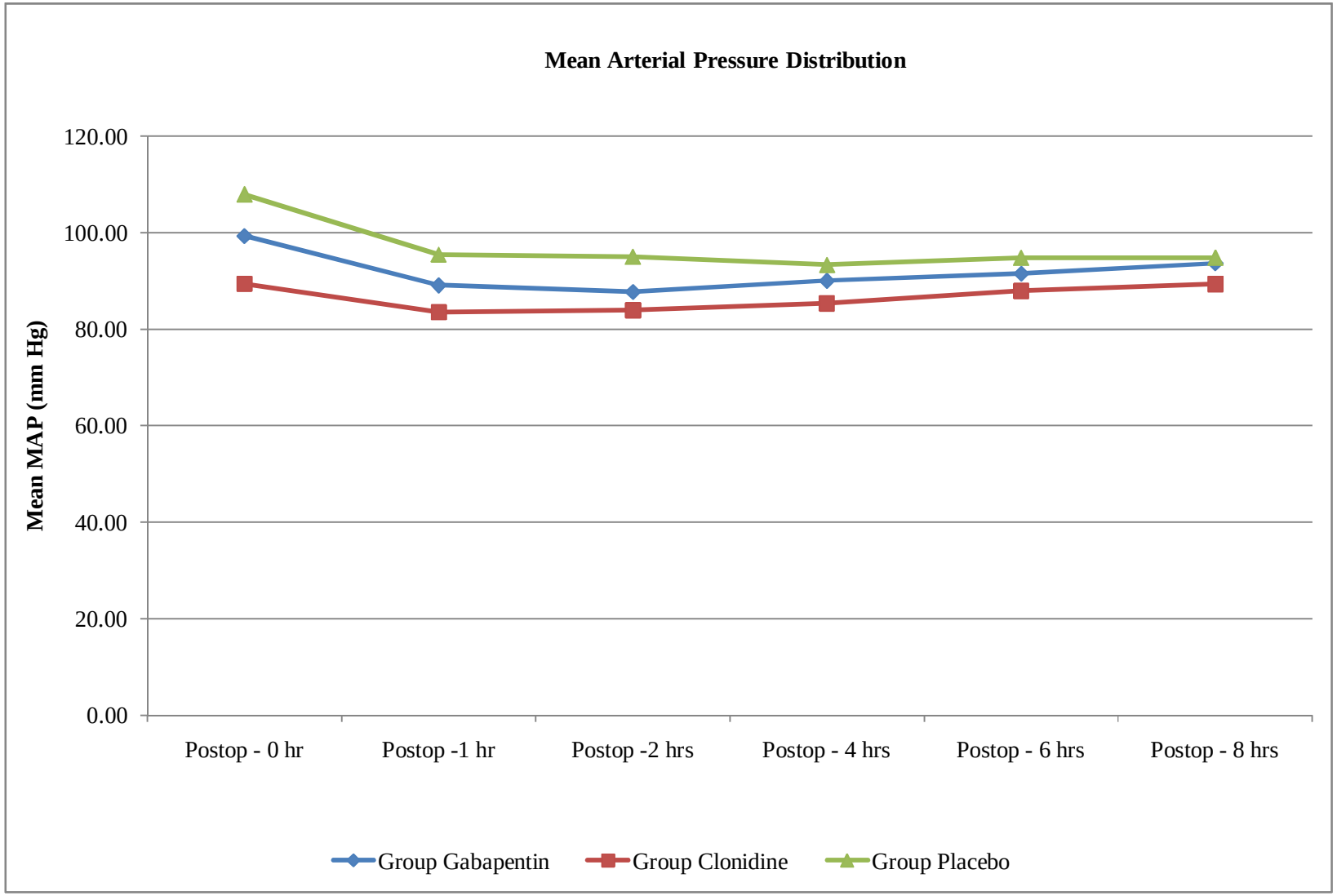
The decreased the mean diastolic blood pressure measurement in group Clonidine compared to the group placebo is statistically significant as the p value is 0.0011 as per unpaired t-test indicating a true difference among study groups.The mean diastolic blood pressure measurement was meaningfully less in group Clonidine compared to group placebo by 14% with a mean difference of 11.45 mm Hg.

This difference is true and significant and has not occurred by chance.

MAP


Mean Arterial Pressure Distribution
Mean MAP (mm Hg)
120.00
100.00
80.00
60.00
40.00
20.00
0.00
Baseline
3 Minutes Prior to Induction
During Induction
During Intubation
1 Minute after Intubation
3 Minutes after Intubation
5 Minutes after Intubation
10 Minutes after Intubation
Group Gabapentin
Group Clonidine
Group Placebo

Mean Arterial Pressure Distribution		Baseline	3 Minutes Prior to Induction	During Induction	During Intubation	1 Minute after Intubation	3 Minutes after Intubation	5 Minutes after Intubation	10 Minutes after Intubation
Group Gabapentin	N	25	25	25	25	25	25	25	25
	Mean	94.00	94.03	90.59	91.73	96.27	93.92	91.87	91.80
	SD	8.62	5.71	6.73	6.02	4.31	5.32	3.64	4.34
Group Clonidine	N	25	24	25	25	25	25	25	25
	Mean	94.32	87.18	87.55	86.26	87.41	86.52	86.35	84.31
	SD	8.23	5.67	4.51	7.83	4.46	5.21	4.95	4.32
Group Placebo	N	25	25	25	25	25	25	25	25
	Mean	93.65	91.59	106.83	101.75	108.20	111.35	105.52	101.35
	SD	7.72	4.98	66.81	44.11	4.81	5.04	4.88	3.87
P value Unpaired t Test	Group Gabapentin vs Group Clonidine	0.8938	0.0001	0.0677	0.0055	0.0000	0.0000	0.0001	0.0000
	Group Gabapentin vs Group Placebo	0.8815	0.0142	0.2381	0.0257	0.0000	0.0000	0.0000	0.0000
	Group Clonidine vs Group Placebo	0.7690	0.0039	0.1628	0.0283	0.0000	0.0000	0.0000	0.0000


Mean Arterial Pressure Distribution
Mean MAP (mm Hg)
120.00
100.00
80.00
60.00
40.00
20.00
0.00
Postop - 0 hr
Postop -1 hr
Postop -2 hrs
Postop - 4 hrs
Postop - 6 hrs
Postop - 8 hrs
Group Gabapentin
Group Clonidine
Group Placebo

Mean Arterial Pressure Distribution		Post-op 0 hr	Post-op 1sthr	Post-op 2nd hr	Post-op 4th hr	Post-op 6 hr	Post-op 8th hr
Group Gabapentin	N	25	25	25	25	25	25
	Mean	99.36	89.12	87.77	90.07	91.53	93.69
	SD	6.26	3.70	3.51	3.62	3.89	3.52
Group Clonidine	N	25	25	25	25	25	25
	Mean	89.37	83.53	83.96	85.35	87.95	89.35
	SD	4.52	5.03	5.10	4.62	5.00	3.36
Group Placebo	N	25	25	25	25	25	25
	Mean	107.95	95.49	95.05	93.36	94.84	94.87
	SD	6.08	4.93	4.65	4.20	4.21	3.49
P value Unpaired t Test	Group Gabapentin vs Group Clonidine	0.0000	0.0001	0.0036	0.0002	0.0069	0.0000
	Group Gabapentin vs Group Placebo	0.0000	0.0000	0.0000	0.0046	0.0059	0.2431
	Group Clonidine vs Group Placebo	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

By conventional criteria the association between the intervention groups and arterial pressure status among study subjects is considered to be statistically significant since $p < 0.05$.

Results

In patients belonging to group Gabapentin, the mean arterial pressure is 92.44 mm Hg. In group Clonidine the mean arterial pressure is 86.54 mm Hg. Similarly in group placebo the mean arterial pressure is 100.63 mm Hg.

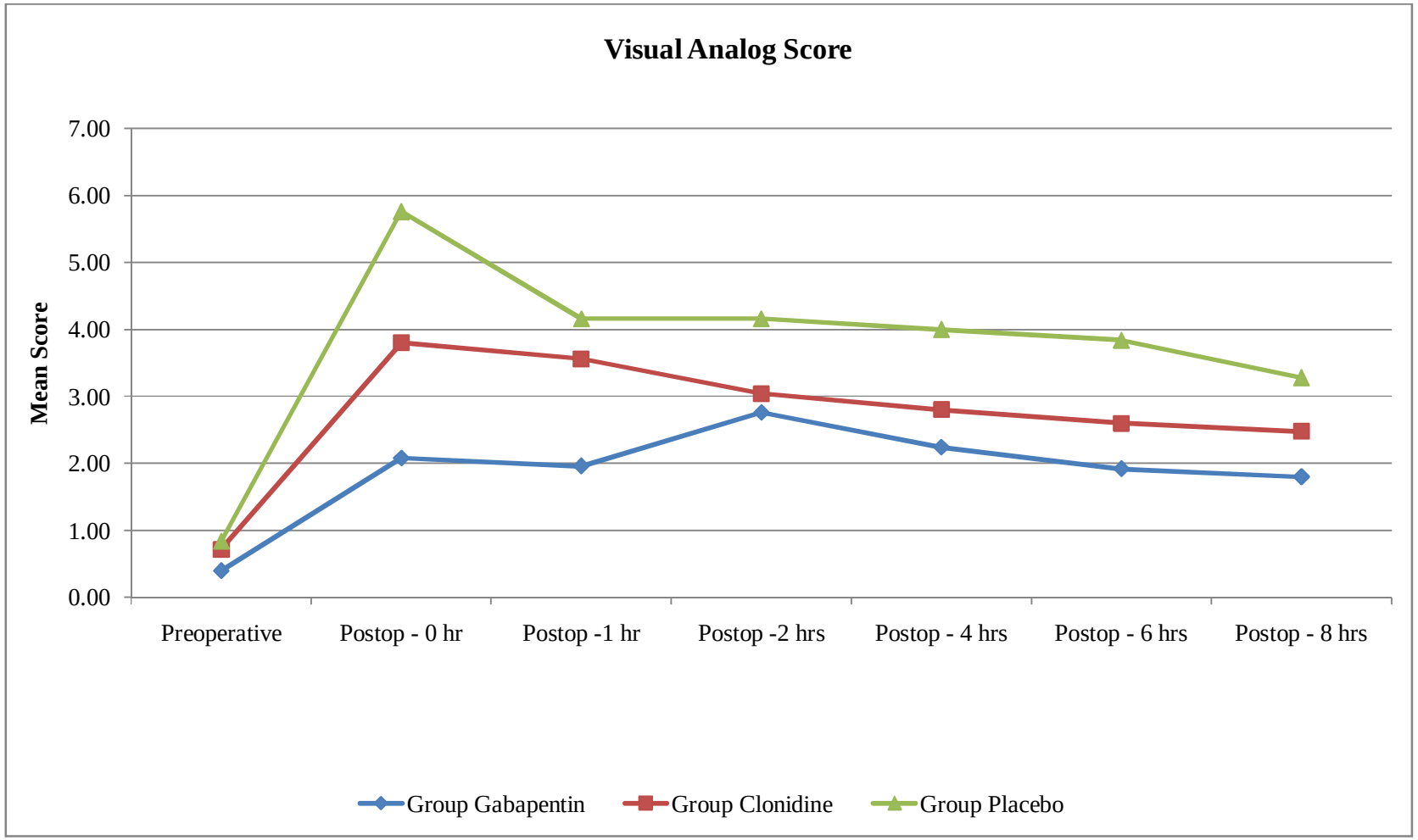
The increased the mean arterial pressure measurement in group Gabapentin compared to the group Clonidine is statistically significant as the p value is 0.0065 as per unpaired t-test indicating a true difference among study groups.The mean arterial pressure measurement was meaningfully more in group Gabapentin compared to group Clonidine by 1.07 times with a mean difference of 5.90 mm Hg.

The decreased the mean arterial pressure measurement in group Gabapentin compared to the group placebo is statistically significant as the p value is 0.0478 as per unpaired t-test indicating a true difference among study groups.The mean arterial pressure measurement was meaningfully less in group Gabapentin compared to group placebo by 8% with a mean difference of 8.18 mm Hg.

The decreased the mean arterial pressure measurement in group Clonidine compared to the group placebo is statistically significant as the p value is 0.0204 as per unpaired t-test indicating a true difference among study groups.The mean arterial pressure measurement was meaningfully less in group Clonidine compared to group placebo by 14% with a mean difference of 14.08 mm Hg.

This difference is true and significant and has not occurred by chance.

VAS


Visual Analog Score
Mean Score
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
Preoperative
Postop - 0 hr
Postop -1 hr
Postop -2 hrs
Postop - 4 hrs
Postop - 6 hrs
Postop - 8 hrs
Group Gabapentin
Group Clonidine
Group Placebo

Visual Analog Score		Pre-op	Post-op 0 hr	Post-op 1sthr	Post-op 2nd hr	Post-op 4th hr	Post-op 6th hr	Post-op 8th hr
Group Gabapentin	N	25	25	25	25	25	25	25
	Mean	0.40	2.08	1.96	2.76	2.24	1.92	1.80
	SD	0.50	0.57	0.54	0.56	0.60	0.40	0.50
Group Clonidine	N	25	25	25	25	25	25	25
	Mean	0.72	3.80	3.56	3.04	2.80	2.60	2.48
	SD	0.46	0.65	0.58	0.73	0.82	0.65	0.59
Group Placebo	N	25	25	25	25	25	25	25
	Mean	0.84	5.76	4.16	4.16	4.00	3.84	3.28
	SD	0.55	1.20	1.11	1.07	0.76	0.62	0.61
P value Unpaired t Test	Group Gabapentin vs Group Clonidine	0.0225	0.0000	0.0000	0.0461	0.0082	0.0001	0.0001
	Group Gabapentin vs Group Placebo	0.0049	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	Group Clonidine vs Group Placebo	0.4081	0.0000	0.0217	0.0001	0.0000	0.0000	0.0000

By conventional criteria the association between the intervention groups and visual analog score among study subjects is considered to be statistically significant since $p < 0.05$.

Results

Inpatients belonging to group Gabapentin, the mean VAS is 1.78 points. In group Clonidine the mean VAS is 2.00 points. Similarly in group placebo the mean VAS is 2.70 points.

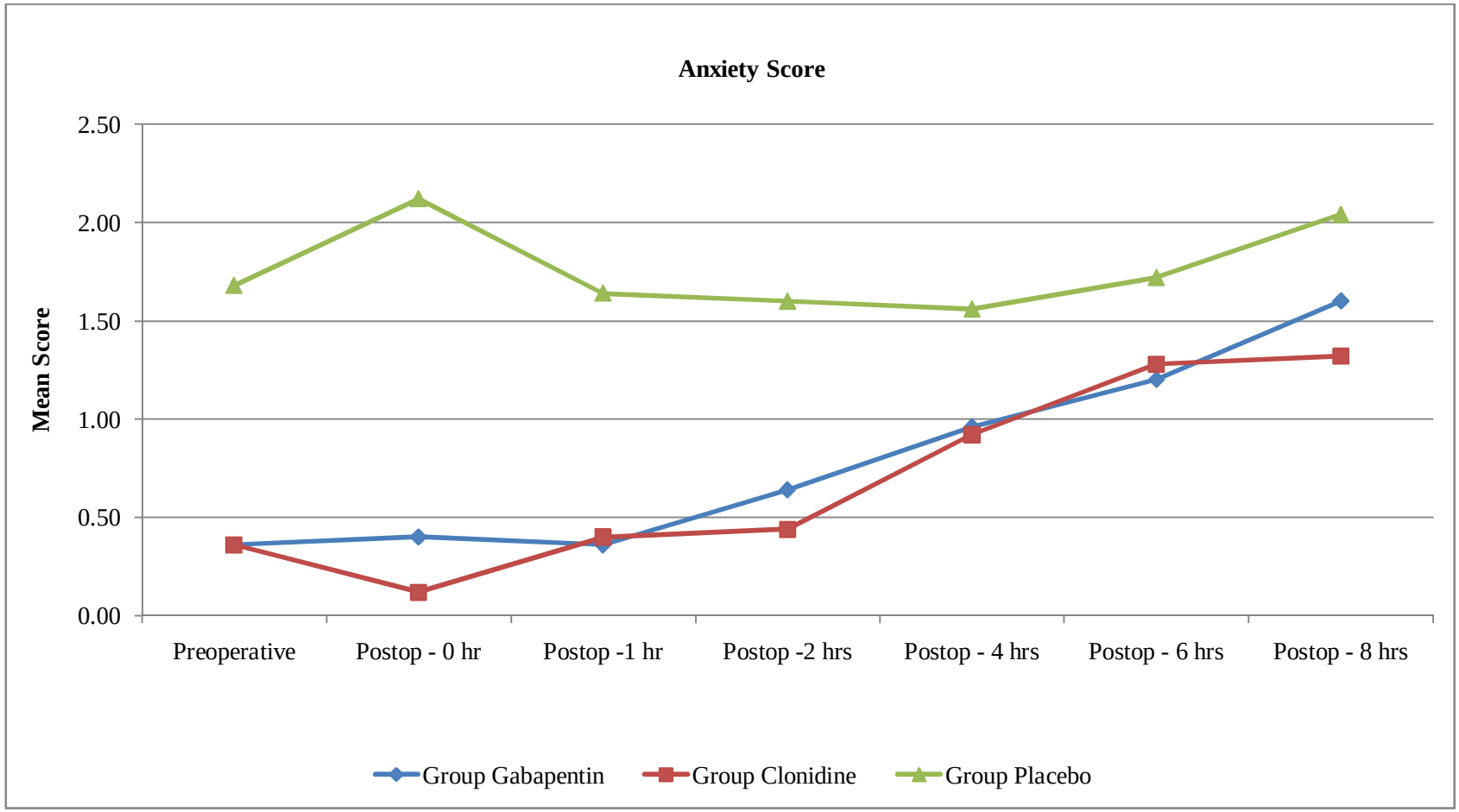
The decreased the mean VAS measurement in group Gabapentin compared to the group Clonidine is statistically significant as the p value is 0.0059 as per unpaired t-test indicating a true difference among study groups. The mean VAS measurement was meaningfully less in group Gabapentin compared to group Clonidine by 11% with a mean difference of 0.22 points.

The decreased the mean VAS measurement in group Gabapentin compared to the group placebo is statistically significant as the p value is 0.0196 as per unpaired t-test indicating a true difference among study groups. The mean VAS measurement was meaningfully less in group Gabapentin compared to group placebo by 34% with a mean difference of 0.91 points.

The decreased the mean VAS measurement in group Clonidine compared to the group placebo is statistically significant as the p value is 0.0254 as per unpaired t-test indicating a true difference among study groups. The mean VAS measurement was meaningfully less in group Clonidine compared to group placebo by 26% with a mean difference of 0.70 points.

This difference is true and significant and has not occurred by chance.

Anxiety Score



Anxiety Score		Pre-op	Post-op 0 hr	Post- op 1sthr	Post-op 2nd hr	Post-op 4th hr	Post-op 6th hr	Post-op 8th hr
Group Gabapentin	N	25	25	25	25	25	25	25
	Mean	0.36	0.40	0.36	0.64	0.96	1.20	1.60
	SD	0.49	0.50	0.49	0.49	0.54	0.41	0.58
Group Clonidine	N	25	25	25	25	25	25	25
	Mean	0.36	0.12	0.40	0.44	0.92	1.28	1.32
	SD	0.49	0.33	0.50	0.51	0.28	0.46	0.48
Group Placebo	N	25	25	25	25	25	25	25
	Mean	1.68	2.12	1.64	1.60	1.56	1.72	2.04
	SD	0.80	0.60	0.50	0.49	0.74	0.58	0.35
P value Unpaired t Test	Group Gabapentin vs Group Clonidine	1.0000	0.0245	0.0163	0.0324	0.0431	0.0177	0.0677
	Group Gabapentin vs Group Placebo	0.0000	0.0000	0.0000	0.0000	0.0004	0.0038	0.0023
	Group Clonidine vs Group Placebo	0.0000	0.0000	0.0000	0.0000	0.0000	0.0153	0.0000

By conventional criteria the association between the intervention groups and Anxiety Score among study subjects is considered to be statistically significant since $p < 0.05$.

Results

In patients belonging to group Gabapentin, the mean Anxiety Score is 0.73 points. In group Clonidine the mean Anxiety Score is 0.68 points. Similarly in group placebo the mean Anxiety Score is 1.41 points.

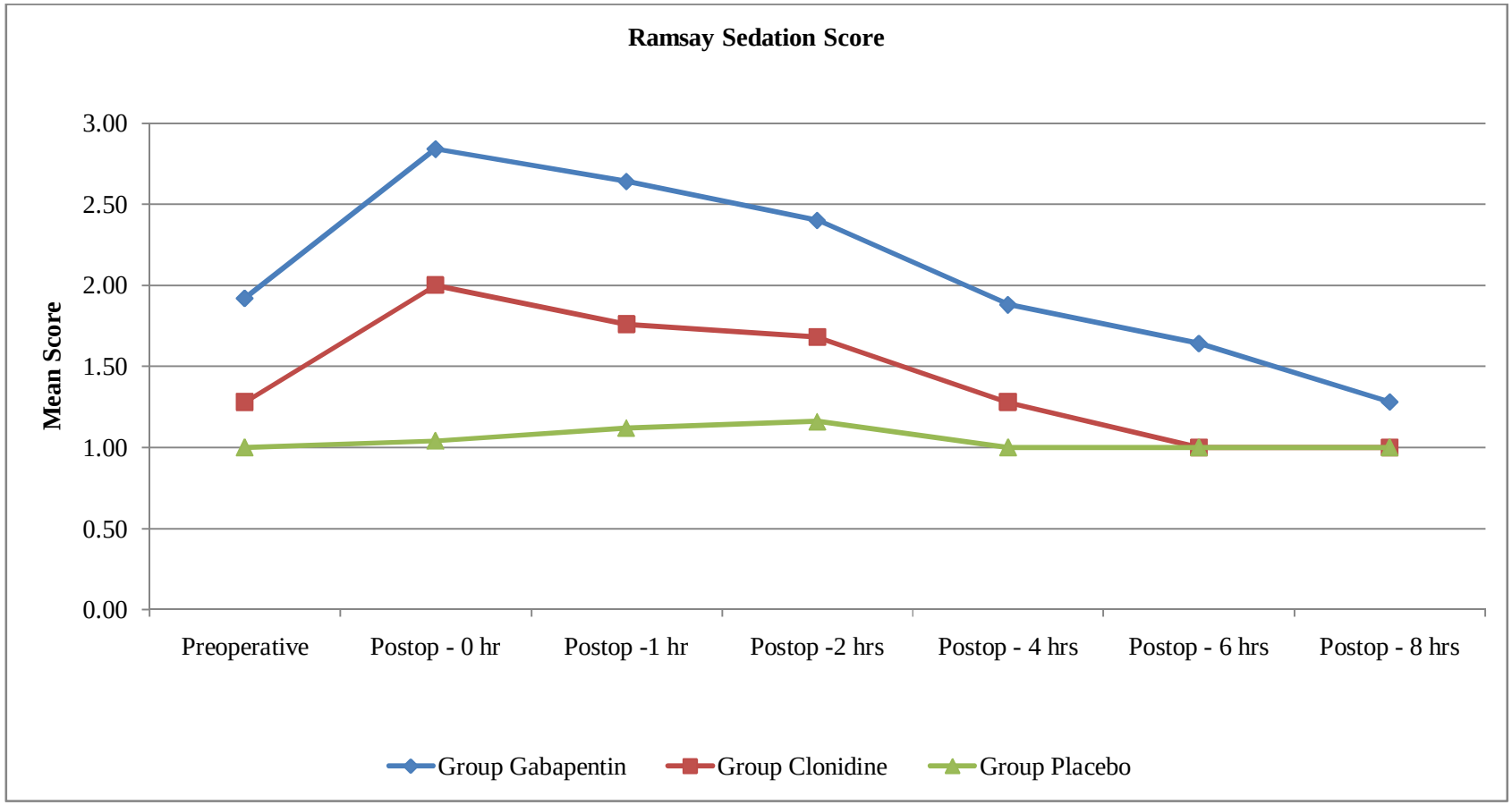
The increased the mean Anxiety Score measurement in group Gabapentin compared to the group Clonidine is statistically significant as the p value is 0.0378 as per unpaired t- test indicating a true difference among study groups. The mean Anxiety Score measurement was meaningfully more in group Gabapentin compared to group Clonidine by 1.08 times with a mean difference of 0.05 points.

The decreased the mean Anxiety Score measurement in group Gabapentin compared to the group placebo is statistically significant as the p value is 0.0082 as per unpaired t- test indicating a true difference among study groups. The mean Anxiety Score measurement was meaningfully less in group Gabapentin compared to group placebo by 48% with a mean difference of 0.68 points.

The decreased the mean Anxiety Score measurement in group Clonidine compared to the group placebo is statistically significant as the p value is 0.0358 as per unpaired t- test indicating a true difference among study groups. The mean Anxiety Score measurement was meaningfully less in group Clonidine compared to group placebo by 52% with a mean difference of 0.73 points.

This difference is true and significant and has not occurred by chance.

Ramsay Sedation Score



Ramsay Sedation Score		Pre-operative	Post –op 0 hr	Post –op 1sthr	Post –op 2nd hr	Post –op 4th hr	Post –op 6th hr	Post- op 8th hr
Group Gabapentin	N	25	25	25	25	25	25	25
	Mean	1.92	2.84	2.64	2.40	1.88	1.64	1.28
	SD	0.76	0.47	0.49	0.58	0.53	0.57	0.54
Group Clonidine	N	25	25	25	25	25	25	25
	Mean	1.28	2.00	1.76	1.68	1.28	1.00	1.00
	SD	0.46	0.58	0.52	0.48	0.46	0.00	0.00
Group Placebo	N	25	25	25	25	25	25	25
	Mean	1.00	1.04	1.12	1.16	1.00	1.00	1.00
	SD	0.00	0.20	0.33	0.37	0.00	0.00	0.00
P value Unpaired t Test	Group Gabapentin vs Group Clonidine	0.0009	0.0000	0.0000	0.0000	0.0001	0.0000	0.0162
	Group Gabapentin vs Group Placebo	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0162
	Group Clonidine vs Group Placebo	0.0054	0.0000	0.0000	0.0001	0.0054	>0.9999	>0.9999

By conventional criteria the association between the intervention groups and Ramsay sedation score among study subjects is considered to be statistically significant since $p < 0.05$.

Results

In patients belonging to group Gabapentin, the mean Ramsay sedation score is 1.89 points. In group Clonidine the mean Ramsay sedation score is 1.31 points. Similarly in group placebo the mean Ramsay sedation score is 1.26 points.

The increased the mean Ramsay sedation score measurement in group Gabapentin compared to the group Clonidine is statistically significant as the p value is 0.0085 as per unpaired t-test indicating a true difference among study groups. The mean Ramsay sedation score measurement was meaningfully more in group Gabapentin compared to group Clonidine by 1.45 times with a mean difference of 0.68 points.

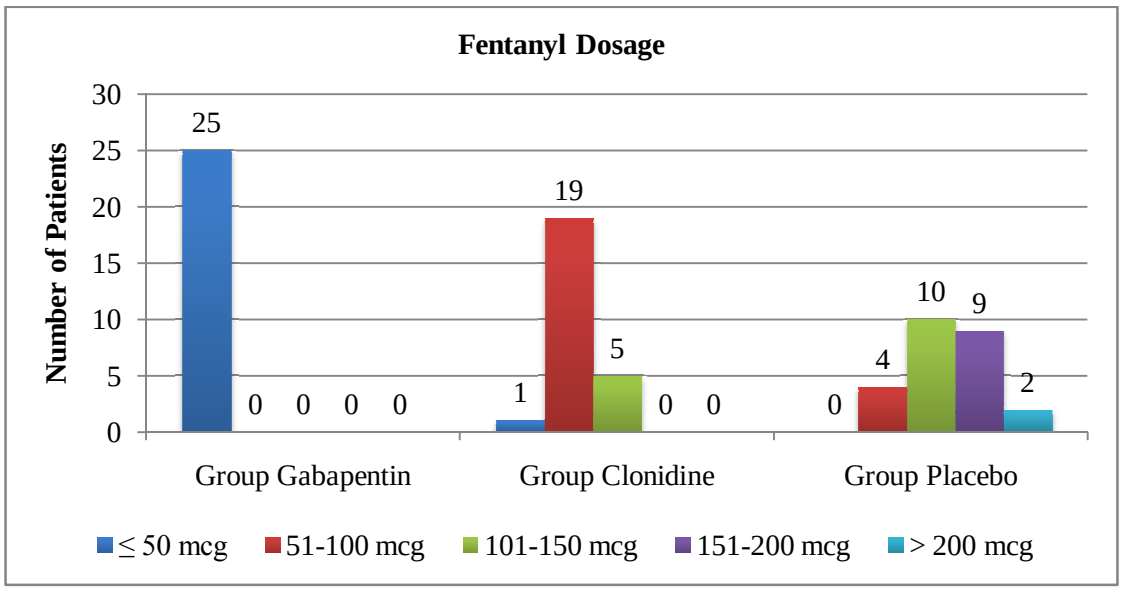
The increased the mean Ramsay sedation score measurement in group Gabapentin compared to the group placebo is statistically significant as the p value is 0.0396 as per unpaired t-test indicating a true difference among study groups. The mean Ramsay sedation score measurement was meaningfully more in group Gabapentin compared to group placebo by 1.51 times with a mean difference of 0.64 points.

The increased the mean Ramsay sedation score measurement in group Clonidine compared to the group placebo is statistically significant as the p value is 0.0162 as per unpaired t- test indicating a true difference among study groups.

The mean Ramsay sedation score measurement was meaningfully more in group Clonidine compared to group placebo by 1.04 times with a mean difference of 0.05 points.

This difference is true and significant and has not occurred by chance.

Fentanyl Dosage



Fentanyl Dosage	Group Gabapentin	%	Group Clonidine	%	Group Placebo	%
≤ 50 mcg	25	100.00	1	4.00	0	0.00
51-100 mcg	0	0.00	19	76.00	4	16.00
101-150 mcg	0	0.00	5	20.00	10	40.00
151-200 mcg	0	0.00	0	0.00	9	36.00
> 200 mcg	0	0.00	0	0.00	2	8.00
Total	25	100.00	25	100.00	25	100.00

Fentanyl Dosage	Group Gabapentin	Group Clonidine	Group Placebo
N	25	25	25
Mean	26.80	89.20	148.40
SD	11.80	19.56	40.38
P value Unpaired t Test	Group Gabapentin vs Group Clonidine		0.0000
	Group Gabapentin vs Group Placebo		0.0000
	Group Clonidine vs Group Placebo		0.0000

By conventional criteria the association between the intervention groups and Fentanyl dosage among study subjects is considered to be statistically significant since $p < 0.05$.

Results

In patients belonging to group Gabapentin, the mean Fentanyl dosage is 26.80 mcg. In group Clonidine the mean Fentanyl dosage is 89.20 mcg. Similarly in group placebo the mean Fentanyl dosage is 148.40 mcg.

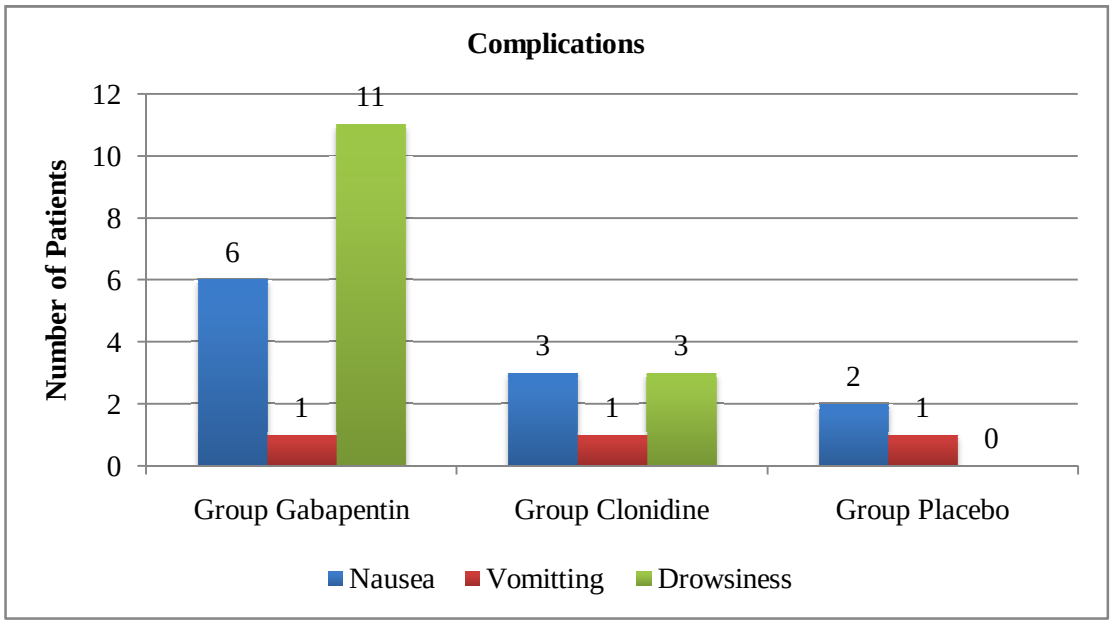
The decreased the mean Fentanyl dosage measurement in group Gabapentin compared to the group Clonidine is statistically significant as the p value is 0.0000 as per unpaired t-test indicating a true difference among study groups. The mean Fentanyl dosage measurement was meaningfully less in group Gabapentin compared to group Clonidine by 70% with a mean difference of 62.40 mcg.

The decreased the mean Fentanyl dosage measurement in group Gabapentin compared to the group placebo is statistically significant as the p value is 0.0000 as per unpaired t-test indicating a true difference among study groups. The mean Fentanyl dosage measurement was meaningfully less in group Gabapentin compared to group placebo by 82% with a mean difference of 121.60 mcg.

The decreased the mean Fentanyl dosage measurement in group Clonidine compared to the group placebo is statistically significant as the p value is 0.0000 as per unpaired t- test indicating a true difference among study groups. The mean Fentanyl dosage measurement was meaningfully more in group Clonidine compared to group placebo by 40% with a mean difference of 59.20 mcg.

This difference is true and significant and has not occurred by chance.

Complications



Complications	Group Gabapentin	%	Group Clonidine	%	Group Placebo	%
Nausea	6	24.00	3	12.00	2	8.00
Vomiting	1	4.00	1	4.00	1	4.00
Drowsiness	11	44.00	3	12.00	0	0.00
Nil	7	28.00	18	72.00	22	88.00
Total	25	100	25	100	25	100
P value Fishers Exact Test		Group Gabapentin Vs Group Clonidine			0.3858	
		Group Gabapentin Vs Group Placebo			0.4696	
		Group Clonidine Vs Group Placebo			0.3430	

Majority of the group Gabapentin patients had drowsiness as complication (n=11, 44%). In the group Clonidine patients, majority had no complication (n=18, 72%). Similarly in the group Placebo patients, majority had no complication (n=22, 88%). The association between the intervention groups and complications status is considered to be not statistically significant since $p > 0.05$ as per chi squared test.

DISSCUSION

Innumerable anaesthetic techniques have been proposed to attenuate the stress response to laryngoscopy and tracheal intubation, with variable grades of success in acute post-operative pain relief. The achievement of good postoperative analgesia as a bonus to the smooth induction with negligible reflex haemodynamic response in the course of laryngoscopy and endotracheal intubation remains an important anaesthetic goal.

This study was done to assess the pre-emptive analgesic effects of two drug namely, Gabapentin 900mg and Clonidine 0.2mg. These two drugs when given orally, have a role in attenuating hemodynamic stress response to laryngoscopy and tracheal intubation and also in decreasing acute postoperative pain relief.

Single dose Gabapentin, when used as pre-treatment prevented dose-dependent development of hyperalgesia and tactile allodynia. In a study by Welty et al[57] found that Gabapentin readily crosses the blood brain barrier and its concentration in brain is nearly similar to that present in blood. So Gabapentin is at its highest concentration in plasma and brain tissue, prevented peripheral and central sensitization by decreasing hyperalgesia and allodynia associated with surgical manipulation by inhibiting membrane voltage gated calcium channels, which is similar to calcium channel blockers[37].The mechanism of Gabapentin which decreases the hemodynamic response to laryngoscopy and tracheal intubation is unknown.[37]

Clonidine is mostly used as an antihypertensive drug and has an analgesic, sedative, and anxiolytic properties.[32, 33]By its central sympatholytic action, it tends to attenuate the hemodynamic response to any surgical stimulus and improve overall

peri-anaesthetic cardiovascular stability and by central α_2 agonist activity, mediates postoperative analgesia.

The doses of these two drugs for pre-emptive analgesia were selected based on previous studies. Those studies used oral Gabapentin in the range of 300-1600mg (in both single and multiple doses), and oral Clonidine in the range of 0.1-0.3 mg. In this study we used 900 mg Gabapentin and 0.2 mg Clonidine orally in line with many authors. The drugs were orally administered 90 minutes prior to induction, as the peak action of both the drugs are known to be 1-2 hours after oral administration.

Variation of heart rate changes decreases with increasing age. Young patients show more extreme changes. Marked fluctuations in hemodynamic response are often seen in geriatric patients. To avoid these above mentioned age related variability, we selected an age range of 18-60 years in our study.

In the present study there were certain changes in all the three groups,

- Heart rate changes were lower in patients with oral Clonidine as compared to the other two groups (However, Gabapentin group swings were less wider than the placebo group).
- Systolic blood pressure, Diastolic blood pressure and the Mean arterial pressure changes were lower in patients with oral Clonidine compared to the other two groups (However oral Gabapentin swings were less wider than the placebo group)
- VAS scoring were much lower in patients with oral Gabapentin compared to the other two groups (Clonidine < placebo group).
- Anxiety Scores were higher in patients with oral placebo compared to other two groups (oral Gabapentin > Clonidine)

- Ramsay sedation scores were higher in patients with oral Gabapentin compared to other two groups (Clonidine > placebo)
- The Fentanyl dosage need was considerably lower in patients with oral Gabapentin compared to other two groups (Clonidine < placebo)

When comparing all the 3 groups i.e. Gabapentin, Clonidine and placebo, there was reduction in haemodynamic response with Clonidine and Gabapentin. This analysis indicates that both Gabapentin and Clonidine have a role in attenuating hemodynamic stress response to laryngoscopy and tracheal intubation and help in maintaining a steady haemodynamic state all throughout the procedure. However there was a tachycardia within acceptable limits with Gabapentin lasting for upto 20-30 minutes post-intubation.

Similarly, when comparing all the groups, there is significantly decreased need for analgesic requirement in both Gabapentin and Clonidine groups than the placebo group.

Our study also proved the role of oral Gabapentin and oral Clonidine in attenuating peri-operative cardiovascular stress responses and decreasing post-operative analgesic requirements, which were verified by many other studies done previously.

Suresh K Singhal et al [45] showed that oral Clonidine 200 μcg when given 90 min before induction, provides good attenuation of hemodynamic response to laryngoscopy and intubation as compared with oral Gabapentin (900 mg), which also fairly obtunded the hypertensive response, but not the tachycardia. In our study also we observed similar findings.

Indira kumara et al[16], have studies the changes in SBP, DBP, MAP and HR following laryngoscopy and intubation after administering Gabapentin 900mg 2 hours before induction. Significant rise in SBP, DBP, MAP was observed following laryngoscopy and tracheal intubation in placebo groups as compared to Gabapentin groups. No significant change in heart rate was documented in both groups.

In a study by **Pandey CK ET al** [31] fentanyl requirement is decreased in patients undergoing lumbar discectomy in Gabapentin group who received 600 mg. Similar results were obtained by **Turan A et al**[51] for spinal surgeries. **Turan A et al** [50] found a decrease in tramadol consumption in patients who were given Gabapentin for abdominal hysterectomy. In other studies by **Fassoulaki A et al,**[7] opioid consumption in post-operative period is decreased

Marashi et al [39], found that after oral administration of 900 mg Gabapentin, 0.2 mg Clonidine, 2 hours before surgery and when compared to a placebo group showed that lowest rates of SBP, DBP, and MAP were seen in Gabapentin group, but Clonidine also had similar blunting effects.

In a study by **Elina M. Tiippana et al** [6], it was found that one dose of Gabapentin orally ranging from 300-1200mg when given preoperatively reduces opioid consumption by 20-60%. They also found that dose of Gabapentin used did not have any outcome on opioid consumption. In this study postoperative VAS score were significantly lesser in Gabapentin group compared to placebo group.

From the above studies most of the authors have used doses ranging from 600-900 mg of Gabapentin, in their studies and found to be effective. In our study we used 900mg Gabapentin and this dose was found to be effective in blunting stress response with regard to HR, SBP, DBP, and MAP.

Barat YK et al, [2] studied the attenuation of heart rate and blood pressure response to laryngoscopy and intubation by Clonidine in 40 healthy patients. Heart rate and blood pressures were significantly lower in the Clonidine group immediately after intubation ($p<0.05$)

Ghignone M et al, [10] studied the effects of oral Clonidine on depths of fentanyl anaesthesia and on cardiovascular response to laryngoscopy and intubation in 24 patients undergoing aorto-coronary bypass surgery and concluded that oral Clonidine reduced the fentanyl requirement and prevented the hemodynamic response to intubation.

Matot et al [24], study shows that, in patients undergoing laparoscopic procedures under general anaesthesia, premedication with oral Clonidine attenuates hemodynamic responses. In our study, premedication with Clonidine 0.2mg administrated 90 minutes before surgery significantly reduced HR, SBP, DBP, and MAP after endotracheal intubation.

According to study conducted by **Mc Lean et al,** [25] use of Gabapentin is associated with side effects like nausea, vomiting, dizziness, confusion, headache, ataxia and weight gain. In a study by **C K Pandey et al** [32] in patients undergoing laparoscopic cholecystectomy it was found that there was higher incidence of sedation in Gabapentin groups of patients.

In our study also, incidence of sedation, nausea and vomiting were more with Gabapentin than other two groups.

The studies conducted by above authors also used similar dosage of Clonidine as we used in our study. With this dose of oral Clonidine 0.2 mg prior to induction, we noticed similar effective blunting of stress response during laryngoscopy and tracheal intubation and noticed similar effectiveness in post-operative pain relief.

SUMMARY

This is a prospective randomised double blinded, case control study with respect to a placebo, to evaluate the pre-emptive analgesic effects of oral Gabapentin 900mg and oral Clonidine 0.2mg on intubation response and post-operative analgesic requirements.

By giving Gabapentin and Clonidine orally 90 minutes preoperatively, it reaches peak concentration in plasma at the onset of surgical stimulus thereby inhibiting central and peripheral neuronal sensitization to pain. By inhibiting the initiation of noxious input it reduces intubation response and post-operative pain intensity and analgesic prerequisites.

Seventy five patients satisfying the inclusion criteria were randomly divided into three groups of twenty five each. Group A received Gabapentin, group B received Clonidine, group C received placebo of vitamin C tablet 90 minutes prior to induction. Intra-operatively patients were monitored for HR, SBP, DBP, and MAP during intubation and post-operatively monitored for sedation, anxiety level, VAS score and total analgesic requirement upto 8 hours. The data derived was evaluated.

Observations of the study were:

- Heart rate changes were lower in patients with oral Clonidine as compared to the other two groups (However, Gabapentin group swings were less wider than the placebo group).
- Systolic blood pressure, Diastolic blood pressure and the Mean arterial pressure changes were lower in patients with oral Clonidine compared to the other two groups (However oral Gabapentin swings were less wider than the placebo group)

- VAS scoring were much lower in patients with oral Gabapentin compared to the other two groups (Clonidine < placebo group).
- Anxiety Scores were higher in patients with oral placebo compared to other two groups (oral Gabapentin > Clonidine)
- Ramsay sedation scores were higher in patients with oral Gabapentin compared to other two groups (Clonidine > placebo)
- The Fentanyl dosage need was considerably lower in patients with oral Gabapentin compared to other two groups (Clonidine < placebo)

CONCLUSION

This study demonstrates that a single oral dose of Gabapentin and Clonidine given pre-operatively, effectively reduces intubation response in elective laparoscopic cholecystectomy. Gabapentin is found to be associated with acceptable tachycardia in $2/3^{rd}$ of this group of patients, persisting for upto 20-30 minutes of intubation. Clonidine is found to be more effective in reducing intubation response compared to both Gabapentin and placebo group.

Both Gabapentin and Clonidine when given orally for pre-emptive analgesia reduced the post-operative pain scores and analgesic requirements in patients undergoing elective laparoscopic cholecystectomy. The incidence of nausea and vomiting were found to be least with Clonidine. Sedation is the only significant side effect observed with Gabapentin in our study.

Thus from our study and from all our findings, both **Gabapentin and Clonidine drugs were found to be effective as good pre-emptive analgesics** in attenuating hemodynamic stress response to laryngoscopy and intubation, with added benefit of providing post-operative pain relief also. **Clonidine was found to be slightly better than Gabapentin in attenuating hemodynamic stress response to laryngoscopy and intubation. Gabapentin was found to be slightly better than Clonidine in providing post-operative pain relief.**

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INFORMATION TO PARTICIPANTS

Investigator: Dr. Kokila.C

Name of the Participant:

Title:

"A Prospective, randomized study comparing the Pre-emptive analgesic effects of oral Gabapentin with oral Clonidine on intubation response and postoperative analgesic requirement for patients undergoing Laparoscopic Cholecystectomy**"**

You are invited to take part in this research study. We have got approval from the IEC. Your are asked to participate because you satisfy the eligibility criteria. We want to compare and study the safety and efficacy of oral Gabapentin and oral Clonidine for intubation response and post-operative pain management in elective Laparoscopic Cholecystectomy

What is the Purpose of the Research:

To compare the analgesic efficacy of oral Gabapentin with Oral Clonidine on intubation response and post-operative analgesic requirement for patients undergoing Laparoscopic Cholecystectomy, based on

Heart rate (HR), Systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP) were measured at baseline (3 min before

induction), just before laryngoscopy, and post-intubation (at 1, 3, 5, and 10 min after starting laryngoscopy).

Post-operative VAS score

Post operative opioid requirement

Dosage of rescue analgesics

The Study Design:

75 Patients presenting for elective Laparoscopic Cholecystectomy were randomly assigned into three groups.

GROUP A (Gabapentin) : received a 900mg tablet orally 90 minutes before anaesthetic induction.

GROUP B (Clonidine) : received a 0.2mg tablet orally 90 minutes before anaesthetic induction.

GROUP C (placebo) : received a placebo capsule orally 90 minutes before anaesthestic induction.

Benefits

The usage of Gabapentin and Clonidine when administered preoperatively, has significant reduction in intubation response, maintains better intra operative hemodynamics, reduces post-operative opioid requirement, thereby significantly reducing the adverse effects of opioids, causes excellent post-operative pain relief.

Discomforts and risks

May cause nausea, vomiting, drowsiness, headache, anaphylactic reactions.

This intervention has been shown to be well tolerated as shown by previous studies. And if you do not want to participate you will have alternative of setting the standard treatment and your safety is our prime concern.

All tests, medicine and medical services concerned with this research will be provided free of cost to the patient.

Time :

Date :

Place :

Signature / Thumb Impression of Patient

Patient Name:

Signature of the Investigator : _____

Name of the Investigator : _____

PATIENT CONSENT FORM

Study Title:

"A Prospective, randomized study comparing the Pre-emptive analgesic effects of oral Gabapentin with oral Clonidine on intubation response and post-operative analgesic requirement for patients undergoing Laparoscopic Cholecystectomy**"**

Study Center:

Institute of Anaesthesiology and Critical Care,

Madras Medicalcollege,

Chennai- 600003.

Participant name : Age: Sex: I.P.No:

I confirm that I have understood the purpose of the above study . I have the opportunity to ask the question and all my questions and doubts have been answered to my satisfaction.

I have been explained about the safety,advantage and disadvantage of the drugs.

I understand that my participation in the study is voluntary and that I am free to withdraw at anytime without giving any reason.

I understand that investigator ,regulatory authorities and the ethical committee will not need my permission to look at my health records both in respect to current

study and any further research that may be conducted in relation to it, even if I withdraw from the study . I understand that my identity will not be revealed in any information released to third parties or published , unless as required under the law . I agree not to restrict the use of any data or results that arise from the study .

Time:

Date: Signature / thumb impression of patient

Place: Patient name:

Signature of the investigator:

Name of the investigator:

PROFORMA

Date : Roll no :

Name :

Age : Ht: Wt: Sex: IP No:

Diagnosis :

Surgical procedure :

PRE OP ASSESSMENT:

HISTORY :

Any Co-morbid illness

H/O Documented Difficult Airway

H/O previous surgeries

EXAMINATION : CVS : Hb :

RS :

MEASURES OF STUDY OUTCOME:

	HR	SBP	DBP	MAP	SPO2
Baseline Parameters					
3 Min Before Induction					
During Induction					
During Intubation					
1 Min After Intubation					
3 Min After Intubation					
5 Min After Intubation					
10 Min After Intubation					

	HR	SBP	DBP	MAP	SPO2	VAS Score	Ramsay Sedation Score	Anxiety Score
Pre-operative								
Post – op 0 Hr								
Post – op 1st Hr								
Post – op 2nd Hr								
Post – op 4th Hr								
Post – op 6th Hr								
Post – op 8th Hr								

COMPLICATIONS IN INTRA OPERATIVE PERIOD:

RESCUE ANALGESICS USED:

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.Kokila.C
II Year PG in MD(Anaesthesiology)
Madras Medical College
Chennai 600 003

Dear Dr.Kokila.C.

The Institutional Ethics Committee has considered your request and approved your study titled **"A PROSPECTIVE , RANDOMIZED STUDY COMPARING THE PREEMPTIVE ANALGESIC EFFECTS OF ORAL GABAPENTIN WITH ORAL CLONIDINE ON INTUBATION RESPONSE AND POST-OPERATIVE ANALGESIC REQUIREMENT FOR PATIENTS UNDERGOING LAPAROSCOPIC CHOLECYSTECTOMY "** NO.06022015.

The following members of Ethics Committee were present in the meeting held on 03.02.2015 conducted at Madras Medical College, Chennai 3.

1. Dr.C.Rajendran, MD	:Chairperson
2. Dr.R.Vimala,MD.,Dean,MMC,Ch-3	: Deputy Chairperson
3. Dr.B.Kalaiselvi,MD.,Vice Principal,MMC,Ch-3	: Member Secretary
4. Dr..R.Nandhini,MD.,Inst.of Pharmacology,MMC	: Member
5. Dr..P.Ragumani, MS., Professor, Inst.of Surgery,MMC	: Member
6. Dr..K.Ramadevi, Director , Inst.of Bio-Chem.MMC	: Member
7. Dr..Saraswathy,MD.,Director,Pathology, MMC	: Member
8. Dr.Md.Ali, MD., DM.,Prof.&HOD of Medl.GE,MD.MMC	: Member
9. Dr.S.G.Sivachidambaram,Director I/c, Inst.of Internal Medicine	: Member
10. Thiru S.Rameshkumar	: Lay Person
11.Thiru S.Govindasamy, BA., BL.,	: Lawyer
12.Tmt.Arnold Saulina, MA., MSW.,	: Social Scientist

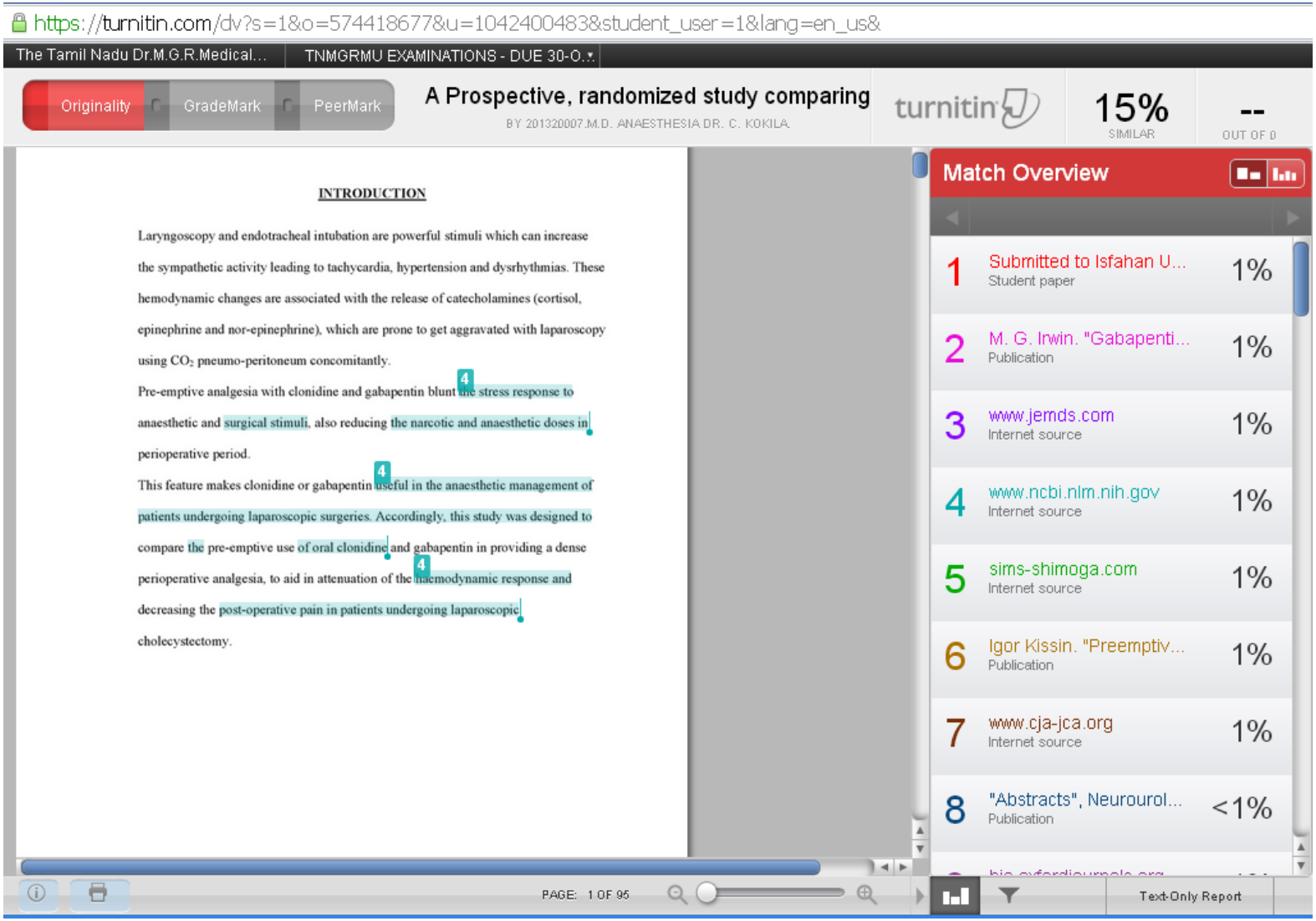
We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Sys 2

Member Secretary - Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003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INTRODUCTION
Laryngoscopy and endotracheal intubation are powerful stimuli which can increase the sympathetic activity leading to tachycardia, hypertension and dysrhythmias. These hemodynamic changes are associated with the release of catecholamines (cortisol, epinephrine and nor-epinephrine), which are prone to get aggravated with laparoscopy using CO_2 pneumo-peritoneum concomitantly.
Pre-emptive analgesia with clonidine and gabapentin blunt the stress response to anaesthetic and surgical stimuli, also reducing the narcotic and anaesthetic doses in perioperative period.
This feature makes clonidine or gabapentin useful in the anaesthetic management of patients undergoing laparoscopic surgeries. Accordingly, this study was designed to compare the pre-emptive use of oral clonidine and gabapentin in providing a dense perioperative analgesia, to aid in attenuation of the haemodynamic response and decreasing the post-operative pain in patients undergoing laparoscopic cholecystectomy.
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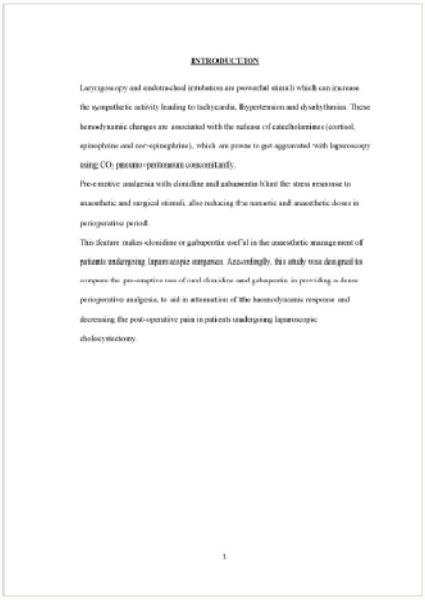

INTRODUCTION

Laryngoscopy and endotracheal intubation are powerful stimuli which can increase the sympathetic activity leading to tachycardia, Hypertension and dysrhythmias. These hemodynamic changes are associated with the release of catecholamines (cortisol, epinephrine and nor-epinephrine), which are prone to get aggravated with laparoscopy using CO_2 pneumo-peritoneum concomitantly.

Pre-emptive analgesia with clonidine and gabapentin blunt the stress response to anaesthetic and surgical stimuli, also reducing the narcotic and anaesthetic doses in perioperative period.

This feature makes clonidine or gabapentin useful in the anaesthetic management of patients undergoing laparoscopic surgeries. Accordingly, this study was designed to compare the pre-emptive use of oral clonidine and gabapentin in providing a dose perioperative analgesia, to aid in attenuation of the haemodynamic response and decreasing the post-operative pain in patients undergoing laparoscopic cholecystectomy.

1

Master Chart

										BASELINE PARAMETERS					3 MINUTES PRIOR TO INDUCTION					DURING INDUCTION			
SL NO	NAME	AGE	SEX	IP NO	WT(kgs)	HT (mts)	BMI	GROUP	ASA	HR	SBP	DBP	MAP	SPO2	HR	SBP	DBP	MAP	SPO2	HR	SBP	DBP	MAP
1	JOTHI	38	F	14382	47	152	20.34	A	1	76	122	74	90	99	79	125	84	97.66666667	99	78	123	82	95.66666667
2	DHANASINGH	60	M	21996	65	172	21.97	A	2	69	126	82	96.66666667	99	68	136	88	104	99	71	132	84	100
3	SELVA KUMAR	47	M	20774	68	168	24.09	A	1	66	122	80	94	99	70	130	84	99.33333333	99	78	133	84	100.3333333
4	KALAVATHY DEVI	50	F	41018	56	158	22.43	A	2	88	134	83	100	99	78	128	79	95.33333333	99	80	130	80	96.66666667
5	BANU	48	F	11756	52	155	21.64	A	2	91	135	87	103	99	80	112	76	88	99	83	105	56	72.33333333
6	PRAMILA	32	F	11468	56	152	24.24	A	1	82	130	88	102	99	75	120	76	90.66666667	99	76	122	74	90
7	AMUDHA	45	F	9839	54	150	24	A	1	89	138	94	108.6666667	99	78	130	86	100.6666667	99	85	128	82	97.33333333
8	AANDI GOWNDAN	45	M	9037	68	169	23.81	A	1	89	142	82	102	99	78	134	86	102	99	78	128	76	93.33333333
9	SARADHA	40	F	12553	54	154	22.77	A	2	85	117	72	87	99	72	122	82	95.33333333	99	71	120	74	89.33333333
10	SAKUNTHALA	60	F	12999	55	160	21.48	A	2	73	145	96	112.3333333	99	72	132	87	102	99	72	134	82	99.33333333
11	MANIKAM	30	M	13912	68	173	22.72	A	1	65	110	75	86.66666667	99	74	122	78	92.66666667	99	72	116	67	83.33333333
12	SHANMUGAPRIYA	38	F	21446	52	153	22.21	A	1	82	130	86	100.6666667	99	76	131	88	102.3333333	99	72	124	83	96.66666667
13	VIJAYALAKSHMI	49	F	18303	57	152	24.67	A	1	78	128	75	92.66666667	99	79	126	82	96.66666667	99	80	120	68	85.33333333
14	MALLIGA	45	F	29900	49	151	21.49	A	2	68	110	68	82	99	72	116	74	88	99	74	115	75	88.33333333
15	BOOPATHY	48	M	19762	69	171	23.6	A	2	72	122	68	86	99	73	117	73	87.66666667	99	70	107	68	81
16	GRACEMARY	33	F	26204	57	157	23.12	A	1	66	112	72	85.33333333	99	70	118	79	92	99	69	120	78	92
17	KUPPU	48	F	27101	57	153	24.35	A	1	78	130	86	100.6666667	99	76	124	82	96	99	71	120	78	92
18	ELSI	39	F	28882	55	158	22.03	A	1	66	109	70	83	99	67	110	74	86	99	74	117	68	84.33333333
19	KALAVATHY	33	F	24158	61	153	24.78	A	1	71	117	75	89	99	73	115	78	90.33333333	99	74	112	68	82.66666667
20	KUTTIAMMAL	50	F	32167	54	148	24.65	A	2	82	124	86	98.66666667	99	77	128	75	92.66666667	99	78	122	82	95.33333333
21	SHANKAR	60	M	34185	65	165	23.88	A	2	64	135	83	100.3333333	99	72	130	84	99.33333333	99	70	123	79	93.66666667
22	TAMIL KUDIYARASAN	25	M	39700	72	174	23.78	A	1	60	109	70	83	99	64	112	75	87.33333333	99	63	110	76	87.33333333
23	PARVATHY	44	F	41474	60	158	24.03	A	1	73	118	84	95.33333333	99	76	120	74	89.33333333	99	72	117	73	87.66666667
24	SHANKAR	60	M	34185	68	172	22.99	A	2	82	116	74	88	99	74	118	74	88.66666667	99	76	120	78	92
25	SHEEBA	40	F	41768	56	152	24.24	A	1	67	109	70	83	99	68	112	74	86.66666667	99	76	118	74	88.66666667
26	RAMACHANDRAN	27	M	39846	65	175	21.22	B	1	64	112	73	86	99	63	110	71	84	99	67	131	79	96.33333333
27	CHITHRA	45	F	10923	59	154	24.88	B	1	69	123	74	90.33333333	99	62	114	67	82.66666667	99	63	117	72	87
28	SHANTHADEVI	42	F	10986	53	156	21.78	B	2	78	140	80	100	99	72	132	76	94.66666667	99	71	128	74	92

29	KAMALA	35	F	10379	57	154	24.03	B	2	82	138	86	103.3333333	99	77	127	68	87.66666667	99	72	122	78	92.66666667
30	VENUGOPAL	60	M	16356	62	169	21.71	B	2	88	130	92	104.6666667	99	74	126	74	91.33333333	99	78	117	72	87
31	NEELAKANDAN	40	M	18393	68	172	22.99	B	1	74	110	70	83.33333333	99	71	106	68	80.66666667	99	70	110	70	83.33333333
32	RAMADURAI	51	M	23493	73	174	24.11	B	1	87	129	72	91	99	81	112	68	82.66666667	99	76	114	76	88.66666667
33	SARASWATHY	35	F	43187	58	158	23.23	B	1	78	128	84	98.66666667	99	80	120	80	93.33333333	99	76	118	80	92.66666667
34	TAMILARASI	31	F	22670	50	152	21.64	B	2	84	130	86	100.6666667	99	70	122	72	88.66666667	99	73	116	75	88.66666667
35	RAMESHBABU	40	M	22581	67	164	24.91	B	1	84	130	86	100.6666667	99	70	112	72	85.33333333	99	74	118	76	90
36	GUNASELAN	24	M	29131	70	169	24.51	B	1	62	104	70	81.33333333	99	64	110	70	83.33333333	99	64	103	64	77
37	TAMILSELVI	38	F	34195	65	154	27.41	B	1	78	124	82	96	99	68	116	73	87.33333333	99	69	112	74	86.66666667
38	SIVAGAMI	56	F	37150	49	153	20.93	B	2	84	112	74	86.66666667	99	64	124	82	96	99	68	123	74	90.33333333
39	JAYAKUMAR	40	M	44830	63	161	24.3	B	1	92	140	92	108	99	76	130	82	98	99	72	126	80	95.33333333
40	MALIGA	58	F	48175	65	155	27.06	B	2	83	133	76	95	99	74	120	68	85.33333333	99	71	122	64	83.33333333
41	MANOHARI	22	F	58508	48	156	19.72	B	1	69	112	72	85.33333333	99	61	109	68	81.66666667	99	62	110	72	84.66666667
42	NAGALAKSHMI	42	F	59256	56	160	21.88	B	1	88	128	74	92	99	78	118	70	86	99	74	116	72	86.66666667
43	MULLAI	33	F	62219	58	161	22.38	B	2	74	118	74	88.66666667	99	69	107	70	82.33333333	99	64	108	74	85.33333333
44	GUNASEELAN	57	M	51037	74	172	25.01	B	1	79	122	76	91.33333333	99	74	118	74		99	73	114	74	87.33333333
45	MANJULA	40	F	57796	54	153	23.07	B	1	84	138	92	107.3333333	99	72	114	70	84.66666667	99	76	118	73	88
46	UMAPATHY	53	F	53834	49	152	21.21	B	2	79	122	86	98	99	72	116	79	91.33333333	99	71	110	74	86
47	DAMODHARAN	58	M	54069	58	161	22.38	B	2	62	112	68	82.66666667	99	64	113	71	85	99	62	110	70	83.33333333
48	SHANTHARUBI	32	F	43331	57	155	23.73	B	1	71	132	84	100	99	68	118	74	88.66666667	99	64	116	73	87.33333333
49	SHARADHA	60	F	42742	53	157	21.5	B	2	65	113	69	83.66666667	99	64	108	64	78.66666667	99	63	107	65	79
50	GUNASUNDARI	42	F	11884	63	162	24.01	B	2	78	138	86	103.3333333	99	72	123	78	93	99	69	122	74	90
51	MAMTHABANU	42	F	12554	57	158	22.83	B	1	87	131	87	101.6666667	99	130	87	101	96.33333333	99	119	80	93	88.66666667
52	VIVEK	24	M	11353	58	169	20.31	C	1	76	122	74	90	99	78	128	78	94.66666667	99	76	125	73	90.33333333
53	KANIGA	32	F	14108	49	156	20.13	C	2	88	132	76	94.66666667	99	84	124	73	90	99	83	1124	78	426.6666667
54	MURUGAESAN	60	M	21800	61	165	22.41	C	1	86	140	92	108	99	84	130	84	99.33333333	99	80	126	86	99.33333333
55	NANDHINI	23	F	15081	51	156	22.96	C	2	65	126	82	96.66666667	99	74	118	76	90	99	70	120	80	93.33333333
56	KURSHINTH	50	F	21105	54	153	23.07	C	2	88	146	92	110	99	78	130	80	96.66666667	99	76	126	82	96.66666667
57	JAYAKAR	49	M	38439	56	157	22.72	C	1	78	124	80	94.66666667	99	69	126	76	92.66666667	99	74	124	71	88.66666667
58	SARASWATHY	32	F	13908	61	159	24.13	C	1	63	130	76	94	99	64	126	78	94	99	67	124	84	97.33333333

59	PUSHPA	45	F	41968	57	154	24.03	C	1	71	131	84	99.66666667	99	73	125	73	90.33333333	99	71	132	86	101.3333333
60	NALINI	25	F	47396	51	157	20.69	C	1	61	110	70	83.33333333	99	63	114	73	86.66666667	99	64	115	74	87.66666667
61	MARIMUTHU	45	M	48819	61	172	20.62	C	2	68	122	76	91.33333333	99	69	117	71	86.33333333	99	62	126	84	98
62	SUDHA	39	F	48636	56	154	23.61	C	1	83	133	74	93.66666667	99	84	134	80	98	99	86	130	76	94
63	FEROZ BEGAM	28	F	51127	47	152	20.34	C	1	81	122	68	86	99	81	121	74	89.66666667	99	78	126	70	88.66666667
64	SUMATHY	30	F	54341	52	155	21.64	C	1	90	144	69	94	99	81	135	72	93	99	84	124	82	96
65	CRYSTAL	35	M	54173	64	176	20.66	C	2	82	124	76	92	99	78	130	78	95.33333333	99	76	123	74	90.33333333
66	KRISHNAKUMARI	48	F	58432	59	156	24.24	C	2	74	106	63	77.33333333	99	73	112	68	82.66666667	99	69	112	79	90
67	LAKSHMI	45	F	59257	53	154	22.35	C	1	82	112	74	86.66666667	99	81	110	70	83.33333333	99	84	116	74	88
76	SAVITHRI	55	F	58537	62	158	24.84	C	2	76	118	68	84.66666667	99	72	120	70	86.66666667	99	74	120	68	85.33333333
69	SUBRAMANI	45	M	59233	74	178	23.36	C	1	61	126	82	96.66666667	99	64	122	74	90	99	63	128	84	98.66666667
70	YASODHA CATHERINE	39	F	62038	54	157	21.91	C	1	68	117	81	93	99	69	126	88	100.6666667	99	70	136	89	104.6666667
71	MAHESHWARI	45	F	60578	56	158	22.43	C	2	79	106	73	84	99	74	112	76	88	99	71	119	80	93
72	PARASURAMAN	55	M	66887	65	174	21.47	C	1	89	118	74	88.66666667	99	84	116	71	86	99	83	123	78	93
73	VASUKI	51	F	45367	59	157	23.94	C	2	92	127	86	99.66666667	99	84	126	84	98	99	80	125	80	95
74	ARUMUGAM	35	M	49079	56	169	19.61	C	1	88	123	87	99	99	76	118	80	92.66666667	99	78	126	81	96
75	NASRIN	37	F	58767	57	150	25.33	C	1	71	128	89	102	99	74	124	71	88.66666667	99	78	122	74	90

	DURING INTUBTION					1 MINUTE AFTER INTUBATION					3 MINUTES AFTER INTUBATION					5 MINUTES AFTER INTUBATION					10 MINUTES AFTER INTUBATION			
SPO2	HR	SBP	DBP	MAP	SP02	HR	SBP	DBP	MAP	SPO2	HR	SBP	DBP	MAP	SPO2	HR	SBP	DBP	MAP	SPO2	HR	SBP	DBP	MAP
99	102	127	84	98.33333333	99	112	132	82	98.66666667	99	107	126	74	91.33333333	99	103	124	78	93.33333333	99	94	122	73	89.33333333
99	90	130	91	104	99	97	132	93	106	99	84	138	90	106	99	82	114	84	94	99	76	119	78	91.66666667
99	96	149	92	111	99	86	119	84	95.66666667	99	85	96	70	78.66666667	99	68	113	78	89.66666667	99	80	122	91	101.3333333
99	100	128	84	98.66666667	99	112	120	86	97.33333333	99	104	128	77	94	99	101	126	76	92.66666667	99	97	117	69	85
99	75	103	64	77	99	79	110	76	87.33333333	99	80	120	84	96	99	84	123	76	91.66666667	99	98	124	78	93.33333333
99	81	125	78	93.66666667	99	98	128	88	101.3333333	99	94	125	80	95	99	87	120	76	90.66666667	99	84	122	75	90.66666667
99	96	124	78	93.33333333	99	100	126	78	94	99	93	127	82	97	99	84	122	70	87.33333333	99	83	124	75	91.33333333
99	102	140	88	105.3333333	99	113	132	88	102.6666667	99	114	133	87	102.3333333	99	104	132	83	99.33333333	99	99	130	86	100.6666667
99	75	122	85	97.33333333	99	81	126	83	97.33333333	99	82	124	72	89.33333333	99	83	125	76	92.33333333	99	76	119	82	94.33333333
99	84	138	94	108.6666667	99	104	136	85	102	99	101	134	84	100.6666667	99	88	132	84	100	99	84	130	81	97.33333333
99	87	124	78	93.33333333	99	92	122	83	96	99	89	125	76	92.33333333	99	86	117	74	88.33333333	99	82	120	70	86.66666667
99	92	122	84	96.66666667	99	116	128	85	99.33333333	99	114	126	84	98	99	111	125	86	99	99	98	124	78	93.33333333
99	84	128	76	93.33333333	99	96	127	83	97.66666667	99	103	130	78	95.33333333	99	96	126	77	93.33333333	99	77	128	78	94.66666667
99	94	126	80	95.33333333	99	105	124	77	92.66666667	99	104	122	78	92.66666667	99	92	121	75	90.33333333	99	86	116	73	87.33333333
99	78	122	75	90.66666667	99	78	130	78	95.33333333	99	79	124	75	91.33333333	99	80	119	76	90.33333333	99	81	120	80	93.33333333
99	80	124	82	96	99	98	127	83	97.66666667	99	101	125	74	91	99	94	120	78	92	99	86	122	76	91.33333333
99	84	126	72	90	99	100	128	78	94.66666667	99	98	120	77	91.33333333	99	90	121	73	89	99	81	124	79	94
99	72	114	72	86	99	86	122	77	92	99	89	123	76	91.66666667	99	82	118	74	88.66666667	99	75	118	69	85.33333333
99	82	120	75	90	99	97	126	83	97.33333333	99	101	122	78	92.66666667	99	99	119	79	92.33333333	99	94	122	76	91.33333333
99	92	128	84	98.66666667	99	115	122	77	92	99	118	130	85	100	99	109	122	82	95.33333333	99	93	125	78	93.66666667
99	92	132	85	100.6666667	99	106	130	84	99.33333333	99	102	126	82	96.66666667	99	100	124	76	92	99	92	120	81	94
99	76	118	79	92	99	90	116	78	90.66666667	99	90	120	76	90.66666667	99	85	113	79	90.33333333	99	76	115	78	90.33333333
99	81	122	78	92.66666667	99	96	123	82	95.66666667	99	92	122	80	94	99	86	120	77	91.33333333	99	76	119	79	92.33333333
99	82	122	76	91.33333333	99	92	124	80	94.66666667	99	99	126	74	91.33333333	99	92	120	72	88	99	91	117	74	88.33333333
99	80	120	76	90.66666667	99	88	120	74	89.33333333	99	81	118	74	88.66666667	99	86	116	70	85.33333333	99	82	112	70	84
99	74	128	66	86.66666667	99	73	113	67	82.33333333	99	64	121	75	90.33333333	99	60	124	82	96	99	67	114	65	81.33333333
99	67	116	71	86	99	69	120	82	94.66666667	99	71	119	79	92.33333333	99	67	122	73	89.33333333	99	68	116	68	84
99	72	127	75	92.33333333	99	71	123	77	92.33333333	99	73	120	71	87.33333333	99	74	118	68	84.66666667	99	71	119	72	87.66666667

99	73	117	72	87	99	76	120	74	89.33333333	99	76	122	80	94	99	78	118	78	91.33333333	99	76	116	80	92
99	76	120	72	88	99	70	116	74	88	99	78	118	76	90	99	74	112	71	84.66666667	99	70	114	71	85.33333333
99	64	102	68	79.33333333	99	72	108	70	82.66666667	99	73	112	72	85.33333333	99	73	114	72	86	99	73	113	71	85
99	77	115	74	87.66666667	99	78	115	78	90.33333333	99	72	113	71	85	99	76	116	73	87.33333333	99	72	110	70	83.33333333
99	102	140	89	106	99	90	139	80	99.66666667	99	84	125	82	96.33333333	99	82	124	80	94.66666667	99	82	118	78	91.33333333
99	72	118	78	91.33333333	99	75	117	78	91	99	75	115	79	91	99	79	119	84	95.66666667	99	75	114	74	87.33333333
99	72	116	74	88	99	74	120	70	86.66666667	99	72	118	76	90	99	75	119	74	89	99	75	116	71	86
99	71	110	68	82	99	72	112	62	78.66666667	99	68	110	63	78.66666667	99	62	112	68	82.66666667	99	64	110	65	80
99	71	120	71	87.33333333	99	72	116	71	86	99	70	115	73	87	99	69	110	70	83.33333333	99	64	112	72	85.33333333
99	69	122	68	86	99	71	124	69	87.33333333	99	68	118	72	87.33333333	99	64	116	71	86	99	69	112	71	84.66666667
99	71	120	80	93.33333333	99	76	118	74	88.66666667	99	71	116	71	86	99	72	114	74	87.33333333	99	71	110	71	84
99	72	120	67	84.66666667	99	74	114	70	84.66666667	99	76	112	68	82.66666667	99	71	117	70	85.66666667	99	70	116	74	88
99	64	108	76	86.66666667	99	65	112	74	86.66666667	99	68	114	72	86	99	64	118	74	88.66666667	99	63	112	64	80
99	76	118	70	86	99	76	116	74	88	99	78	114	72	86	99	76	116	68	84	99	74	115	69	84.33333333
99	72	110	70	83.33333333	99	78	118	71	86.66666667	99	74	113	74	87	99	72	108	68	81.33333333	99	69	107	63	77.66666667
99	71	108	68	81.33333333	99	76	110	70	83.33333333	99	72	112	72	85.33333333	99	68	114	73	86.66666667	99	71	110	68	82
99	78	114	71	85.33333333	99	75	113	69	83.66666667	99	74	118	73	88	99	71	116	74	88	99	73	112	68	82.66666667
99	74	112	76	88	99	74	114	74	87.33333333	99	72	110	70	83.33333333	99	73	108	68	81.33333333	99	70	109	67	81
99	65	108	72	84	99	64	112	71	84.66666667	99	64	96	62	73.33333333	99	60	94	68	76.66666667	99	57	100	64	76
99	69	120	79	92.66666667	99	70	118	75	89.33333333	99	67	117	76	89.66666667	99	68	115	70	85	99	71	117	78	91
99	66	112	72	85.33333333	99	65	110	68	82	99	68	98	64	75.33333333	99	67	102	63	76	99	62	101	66	77.66666667
99	75	125	78	93.66666667	99	76	124	75	91.33333333	99	75	121	68	85.66666667	99	67	118	72	87.33333333	99	68	122	74	90
99	102	149	100	116.3333333	99	87	138	98	111.3333333	99	86	128	89	102	99	90	123	85	97.66666667	99	90	121	84	96.33333333
99	88	140	90	106.6666667	99	90	146	94	111.3333333	99	99	148	99	115.3333333	99	102	140	82	101.3333333	99	100	130	84	99.33333333
99	98	138	88	104.6666667	99	104	155	89	111	99	108	150	84	106	99	100	134	83	100	99	93	129	81	97
99	94	133	84	100.3333333	99	112	142	96	111.3333333	99	115	150	98	115.3333333	99	120	152	98	116	99	118	146	92	110
99	88	136	88	104	99	99	142	92	108.6666667	99	104	148	96	113.3333333	99	110	144	90	108	99	102	133	86	101.6666667
99	83	137	83	101	99	98	149	89	109	99	104	160	104	122.6666667	99	116	145	90	108.3333333	99	112	143	90	107.6666667
99	84	124	76	92	99	101	138	90	106	99	111	142	92	108.6666667	99	116	146	91	109.3333333	99	102	130	90	103.3333333
99	78	138	84	102	99	84	142	94	110	99	99	138	90	106	99	101	136	86	102.6666667	99	108	134	84	100.6666667

99	83	140	88	105.3333333	99	94	153	92	112.3333333	99	106	154	102	119.3333333	99	112	146	94	111.3333333	99	114	144	88	106.6666667
99	73	126	86	99.33333333	99	92	140	90	106.6666667	99	103	142	94	110	99	98	146	86	106	99	96	138	82	100.6666667
99	86	122	81	94.66666667	99	101	111	84	93	99	114	142	92	108.6666667	99	115	145	94	111	99	112	141	87	105
99	92	140	88	105.3333333	99	100	142	92	108.6666667	99	104	148	92	110.6666667	99	98	138	89	105.3333333	99	96	133	84	100.3333333
99	86	138	84	102	99	99	145	96	112.3333333	99	102	148	97	114	99	104	142	86	104.6666667	99	97	136	81	99.33333333
99	86	132	80	97.33333333	99	88	138	86	103.3333333	99	98	146	88	107.3333333	99	101	143	86	105	99	96	139	87	104.3333333
99	89	144	91	108.6666667	99	108	141	93	109	99	113	146	92	110	99	103	140	86	104	99	101	134	85	101.3333333
99	78	138	76	96.66666667	99	98	144	86	105.3333333	99	108	149	90	109.6666667	99	112	137	85	102.3333333	99	96	136	87	103.3333333
99	92	130	86	100.6666667	99	98	138	89	105.3333333	99	112	144	92	109.3333333	99	108	142	87	105.3333333	99	100	138	81	100
99	81	128	78	94.66666667	99	89	143	91	108.3333333	99	103	148	98	114.6666667	99	110	146	95	112	99	101	133	89	103.6666667
99	74	133	88	103	99	109	150	101	117.3333333	99	112	145	95	111.6666667	99	100	138	86	103.3333333	99	83	127	81	96.33333333
99	79	145	90	108.3333333	99	98	148	94	112	99	104	150	100	116.6666667	99	94	136	81	99.33333333	99	86	130	79	96
99	86	126	84	98	99	108	139	99	112.3333333	99	114	145	94	111	99	107	138	88	104.6666667	99	96	136	84	101.3333333
99	86	133	86	101.6666667	99	90	146	90	108.6666667	99	96	143	88	106.3333333	99	94	140	80	100	99	89	134	84	100.6666667
99	91	132	88	102.6666667	99	104	142	86	104.6666667	99	110	149	98	115	99	96	141	95	110.3333333	99	88	131	85	100.3333333
99	84	134	85	101.3333333	99	99	140	91	107.3333333	99	112	156	98	117.3333333	99	98	148	94	112	99	84	142	86	104.6666667
99	84	124	78	93.33333333	99	88	139	80	99.66666667	99	94	140	84	102.6666667	99	90	136	79	98	99	86	133	74	93.66666667

	POST OPERATIVE HEART RATE						POST OPERATIVE SYSTOLIC BP						POST OPERATIVE DIASTOLIC BP						POST OPERATIVE MAP				
SPO2	0 HR	1 HR	2 HR	4 HR	6 HR	8 HR	0 HR	1 HR	2 HR	4 HR	6 HR	8 HR	0 HR	1 HR	2 HR	4 HR	6 HR	8 HR	0 HR	1HR	2HR	4 HR	6HR
99	86	75	79	78	76	79	138	124	120	123	132	130	82	78	76	82	80	86	100.6666667	93.33333333	90.66666667	95.66666667	97.33333333
99	92	72	68	69	72	73	144	120	118	117	120	123	92	75	74	78	76	75	109.3333333	90	88.66666667	91	90.66666667
99	94	76	81	69	71	72	142	120	126	119	122	128	92	81	76	74	75	76	108.6666667	94	92.66666667	89	90.66666667
99	86	80	83	74	81	82	126	122	112	116	125	126	82	84	75	75	72	79	96.66666667	96.66666667	87.33333333	88.66666667	89.66666667
99	103	90	75	78	73	74	130	120	124	123	125	127	84	76	75	71	73	79	99.33333333	90.66666667	91.33333333	88.33333333	90.33333333
99	98	82	85	73	74	78	137	125	120	122	123	117	90	81	69	77	76	83	105.6666667	95.66666667	86	92	91.66666667
99	89	76	77	76	82	73	129	118	113	121	119	123	86	72	68	71	75	81	100.3333333	87.33333333	83	87.66666667	89.66666667
99	93	89	84	87	84	82	147	120	122	124	132	126	96	76	75	76	82	83	113	90.66666667	90.66666667	92	98.66666667
99	91	77	76	73	75	77	132	120	111	118	121	122	87	72	65	73	74	78	102	88	80.33333333	88	89.66666667
99	99	78	76	77	81	78	140	124	127	130	131	130	97	72	74	75	81	84	111.3333333	89.33333333	91.66666667	93.33333333	97.66666667
99	97	74	82	77	79	81	124	114	115	114	119	124	76	67	68	71	71	70	92	82.66666667	83.66666667	85.33333333	87
99	88	72	76	78	76	83	135	118	123	124	122	117	84	68	72	72	74	81	101	84.66666667	89	89.33333333	90
99	90	82	81	81	68	84	130	116	122	126	121	124	86	74	76	84	80	81	100.6666667	88	91.33333333	98	93.66666667
99	89	76	77	76	75	77	128	117	112	119	118	122	74	76	69	75	76	77	92	89.66666667	83.33333333	89.66666667	90
99	91	65	69	78	79	75	126	118	119	123	127	120	77	68	70	75	80	77	93.33333333	84.66666667	86.33333333	91	95.66666667
99	89	67	67	75	76	74	128	117	118	115	120	121	83	67	69	72	78	76	98	83.66666667	85.33333333	86.33333333	92
99	87	78	76	69	78	76	134	122	121	124	126	132	76	75	76	80	84	83	95.33333333	90.66666667	91	94.66666667	98
99	80	75	68	76	75	74	126	117	116	116	120	122	78	72	69	80	74	80	94	87	84.66666667	92	89.33333333
99	76	68	71	76	78	79	122	117	109	116	118	120	76	74	68	82	75	76	91.33333333	88.33333333	81.66666667	93.33333333	89.33333333
99	82	77	78	77	82	81	126	118	119	120	127	126	83	76	74	75	80	82	97.33333333	90	89	90	95.66666667
99	85	77	76	80	81	80	138	117	122	120	119	120	86	78	77	81	77	82	103.3333333	91	92	94	91
99	79	77	67	65	64	68	122	115	116	110	117	114	82	67	72	74	69	71	95.33333333	83	86.66666667	86	85
99	82	81	77	78	76	82	124	122	117	118	123	127	80	78	76	72	79	80	94.66666667	92.66666667	89.66666667	87.33333333	93.66666667
99	89	82	76	75	73	80	128	120	118	116	118	121	78	71	74	72	68	75	94.66666667	87.33333333	88.66666667	86.66666667	84.66666667
99	84	73	71	73	69	76	122	115	119	115	120	123	80	76	75	66	71	76	94	89	89.66666667	82.33333333	87.33333333
99	87	72	75	79	76	74	125	110	112	111	115	111	84	64	67	68	72	73	97.66666667	79.33333333	82	82.33333333	86.33333333
99	74	65	65	67	63	67	118	116	115	120	118	116	72	70	80	69	68	74	87.33333333	85.33333333	91.66666667	86	84.66666667
99	67	76	66	72	73	70	117	115	119	120	122	118	72	74	68	79	78	74	87	87.66666667	85	92.66666667	92.66666667

99	78	80	76	72	71	75	118	113	115	117	120	121	78	68	69	72	78	76	91.33333333	83	84.33333333	87	92
99	78	68	69	70	69	71	116	108	109	108	110	112	72	67	65	68	64	73	86.66666667	80.66666667	79.66666667	81.33333333	79.33333333
99	78	71	69	72	73	68	116	109	106	112	114	110	72	68	67	67	71	73	86.66666667	81.66666667	80	82	85.33333333
99	81	76	74	69	73	76	118	112	110	109	115	118	78	67	68	64	72	75	91.33333333	82	82	79	86.33333333
99	87	86	88	82	83	79	128	124	120	116	117	122	72	71	68	74	72	73	90.66666667	88.66666667	85.33333333	88	87
99	76	75	80	76	78	76	132	122	117	115	118	124	68	60	71	73	74	76	89.33333333	80.66666667	86.33333333	87	88.66666667
99	86	82	80	76	81	82	125	118	120	121	119	123	76	69	68	73	76	78	92.33333333	85.33333333	85.33333333	89	90.33333333
99	72	67	72	74	69	72	123	112	115	116	123	118	78	67	64	62	87	78	93	82	81	80	99
99	69	72	78	78	75	76	117	118	114	122	128	119	70	68	67	69	70	71	85.66666667	84.66666667	82.66666667	86.66666667	89.33333333
99	67	76	75	73	69	76	115	120	122	121	117	119	67	68	72	75	74	72	83	85.33333333	88.66666667	90.33333333	88.33333333
99	75	78	80	76	75	81	132	124	122	121	124	126	80	76	77	74	73	76	97.33333333	92	92	89.66666667	90
99	84	76	75	77	72	71	127	116	118	119	120	117	68	78	78	71	75	77	87.66666667	90.66666667	91.33333333	87	90
99	71	62	60	62	64	66	117	96	99	101	105	110	68	61	69	65	67	70	84.33333333	72.66666667	79	77	79.66666667
99	68	68	62	64	70	68	122	116	118	114	115	118	78	70	73	68	71	79	92.66666667	85.33333333	88	83.33333333	85.66666667
99	72	71	67	70	74	80	118	110	106	107	102	110	64	63	67	69	72	71	82	78.66666667	80	81.66666667	82
99	76	70	68	64	65	69	123	109	103	115	120	121	78	67	59	64	67	74	93	81	73.66666667	81	84.66666667
99	78	73	61	68	69	68	118	110	112	117	116	120	65	64	71	74	84	83	82.66666667	79.33333333	84.66666667	88.33333333	94.66666667
99	73	64	61	62	65	67	117	98	96	102	104	111	72	60	64	66	65	71	87	72.66666667	74.66666667	78	78
99	67	63	63	61	64	65	110	112	104	108	114	116	74	68	64	73	78	76	86	82.66666667	77.33333333	84.66666667	90
99	74	71	72	71	69	78	119	115	120	117	113	120	73	72	68	71	78	75	88.33333333	86.33333333	85.33333333	86.33333333	89.66666667
99	74	67	63	61	74	79	124	118	116	119	120	123	82	76	74	78	75	81	96	90	88	91.66666667	90
99	65	67	66	63	64	67	128	120	117	121	123	122	79	76	78	80	81	79	95.33333333	90.66666667	91	93.66666667	95
99	115	92	98	92	84	83	148	136	138	129	130	132	98	94	88	76	78	84	114.6666667	108	104.6666667	93.66666667	95.33333333
99	105	98	76	78	88	83	140	127	125	132	126	132	95	82	81	76	83	83	110	97	95.66666667	94.66666667	97.33333333
99	109	92	86	83	81	83	145	132	133	125	126	125	89	78	79	83	81	81	107.6666667	96	97	97	96
99	105	95	83	84	82	81	138	132	132	128	135	134	90	83	82	80	80	79	106	99.33333333	98.66666667	96	98.33333333
99	96	72	68	65	68	67	132	125	122	121	124	120	80	73	71	76	80	75	97.33333333	90.33333333	88	91	94.66666667
99	112	92	88	83	84	82	148	133	136	124	125	122	100	87	83	82	83	84	116	102.3333333	100.6666667	96	97
99	108	94	80	74	73	71	137	124	126	122	119	124	85	82	78	76	69	80	102.3333333	96	94	91.33333333	85.66666667
99	96	87	75	74	72	69	137	120	118	119	125	127	83	81	82	75	82	80	101	94	94	89.66666667	96.33333333

99	98	82	78	79	84	83	146	132	134	128	127	133	92	81	82	84	82	80	110	98	99.33333333	98.66666667	97
99	103	75	72	80	82	73	130	122	126	125	128	120	84	74	72	73	77	71	99.33333333	90	90	90.33333333	94
99	108	78	73	79	67	77	134	126	124	118	124	126	85	72	71	67	75	79	101.3333333	90	88.66666667	84	91.33333333
99	105	85	88	85	83	80	157	137	132	124	135	132	101	87	84	86	87	80	119.6666667	103.6666667	100	98.66666667	103
99	97	80	84	82	81	86	138	127	126	126	132	131	87	78	82	82	81	79	104	94.33333333	96.66666667	96.66666667	98
99	112	90	85	84	83	84	155	134	135	132	128	129	103	88	85	83	82	81	120.3333333	103.3333333	101.6666667	99.33333333	97.33333333
99	101	79	88	87	89	80	138	127	128	130	124	125	88	76	82	81	83	82	104.6666667	93	97.33333333	97.33333333	96.66666667
99	99	75	82	83	76	78	135	120	122	124	119	121	87	76	75	72	75	71	103	90.66666667	90.66666667	89.33333333	89.66666667
99	110	83	84	85	83	86	143	127	126	127	123	128	93	78	74	72	76	79	109.6666667	94.33333333	91.33333333	90.33333333	91.66666667
99	98	76	76	80	81	79	137	125	123	122	128	125	88	78	78	82	81	74	104.3333333	93.66666667	93	95.33333333	96.66666667
99	76	64	60	73	75	76	147	123	124	119	112	126	94	80	74	73	79	82	111.6666667	94.33333333	90.66666667	88.33333333	90
99	97	74	75	73	79	76	142	126	132	120	118	120	91	74	83	81	79	76	108	91.33333333	99.33333333	94	92
99	89	73	72	78	82	81	140	117	115	119	112	118	92	76	78	69	73	75	108	89.66666667	90.33333333	85.66666667	86
99	114	90	86	89	83	84	142	122	126	124	127	123	95	83	82	83	84	81	110.6666667	96	96.66666667	96.66666667	98.33333333
99	104	83	78	76	78	80	138	120	117	126	125	123	86	73	72	71	80	81	103.3333333	88.66666667	87	89.33333333	95
99	90	80	82	83	79	86	140	128	124	123	121	125	102	82	81	79	78	83	114.6666667	97.33333333	95.33333333	93.66666667	92.33333333
99	112	80	87	90	92	88	145	132	121	127	134	130	94	78	83	82	85	82	111	96	95.66666667	97	101.3333333

	VAS SCORING							ANXIETY SCORE							RAMSAY SEDATION SCORE							FENTANYL (mcg)	COMPLICATIONS		
8 HR	PRE OP	0 HR	1 HR	2 HR	4 HR	6 HR	8 HR	PREOP	OHR	1HR	2HR	4HR	6HR	8HR	PRE OP	0 HR	1 HR	2 HR	4 HR	6HR	8 HR		NAUSEA	VOMITTING	DROWSINESS
100.6666667	1	3	1	2	2	2	2	0	0	1	1	0	1	1	1	3	3	3	3	3	3	10	A	A	P
91	1	3	2	4	2	2	2	0	0	0	1	0	1	2	2	4	3	3	3	2	2	20	A	A	P
93.33333333	0	2	1	2	1	1	1	0	1	0	0	0	2	2	2	2	2	2	2	2	1	10	A	A	A
94.66666667	1	2	2	2	3	2	2	0	0	0	0	1	1	3	1	3	3	3	2	2	1	30	A	A	A
95	0	2	2	3	2	1	1	0	1	0	0	1	1	2	1	3	3	2	2	2	1	20	A	A	A
94.33333333	1	1	2	3	3	2	2	1	0	0	1	1	1	1	3	2	3	3	2	2	1	20	P	A	P
95	1	2	3	3	2	2	2	1	1	0	0	1	2	2	1	2	2	1	1	1	1	40	A	A	A
97.33333333	0	2	3	3	2	2	2	0	1	1	1	2	1	2	2	2	2	3	2	2	2	30	A	A	A
92.66666667	0	1	2	3	2	2	2	0	1	0	0	1	1	1	2	3	3	3	2	2	1	10	P	A	A
99.33333333	1	2	2	3	2	2	2	1	0	0	1	1	1	2	3	3	2	2	1	1	1	10	A	A	P
88	0	2	1	3	2	2	3	1	0	1	1	0	1	2	1	3	3	3	2	2	2	30	A	A	P
93	0	2	3	3	2	2	2	1	1	0	1	2	1	1	2	3	3	3	2	2	2	40	P	P	P
95.33333333	1	2	2	4	2	2	2	0	0	0	1	1	2	1	2	3	2	2	1	1	1	50	P	A	A
92	0	2	2	3	2	2	2	0	1	1	1	2	1	1	2	3	2	2	2	1	1	30	A	A	P
91.33333333	0	2	2	3	2	2	2	0	0	0	1	1	2	2	2	3	3	2	2	2	1	20	A	A	A
91	0	1	2	3	3	2	2	0	0	0	1	1	1	2	3	3	3	2	2	2	2	40	A	A	A
99.33333333	0	2	2	2	3	3	2	0	0	1	1	1	1	2	1	3	2	2	1	1	1	40	P	A	A
94	1	2	2	3	2	2	2	1	1	0	0	1	1	1	2	3	3	2	2	2	1	20	A	A	P
90.66666667	0	2	1	2	3	2	2	0	0	1	1	1	1	1	2	3	3	3	2	2	1	10	A	A	P
96.66666667	1	3	2	2	4	2	2	1	1	1	1	1	2	2	1	3	2	2	2	1	1	40	A	A	A
94.66666667	1	2	2	3	2	2	1	1	0	1	0	1	1	2	3	3	3	3	2	1	1	30	A	A	P
85.33333333	0	3	2	2	2	2	1	0	1	0	1	1	1	2	3	3	3	3	2	2	1	30	A	A	A
95.66666667	0	3	2	2	2	1	2	0	0	1	1	1	1	1	1	2	2	2	1	1	1	30	A	A	A
90.33333333	0	2	2	3	2	2	1	1	0	0	0	1	1	1	3	3	3	2	2	1	1	40	A	A	A
91.66666667	0	2	2	3	2	2	1	0	0	0	0	1	1	1	2	3	3	2	2	1	1	20	P	A	P
85.66666667	1	4	3	2	2	2	3	0	1	0	1	1	1	1	2	3	3	2	2	1	1	50	A	A	P
88	1	3	4	2	2	3	3	0	0	0	0	1	1	1	1	1	1	1	1	1	1	70	A	A	A
88.66666667	1	4	3	3	2	3	3	0	0	1	1	1	1	1	1	2	2	2	1	1	1	80	A	A	A

91	0	4	3	3	3	2	2	0	0	0	1	1	1	1	1	2	2	1	1	1	1	100	A	A	A
86	1	4	4	3	2	2	2	0	0	0	1	1	2	2	2	2	1	1	1	1	1	110	A	A	A
85.33333333	1	3	4	3	2	2	3	1	0	0	0	1	1	1	1	2	2	1	1	1	1	110	A	A	A
89.33333333	1	4	3	3	2	2	3	1	0	0	0	1	1	2	1	2	2	2	1	1	1	90	A	A	A
89.33333333	0	5	4	3	3	3	3	0	0	0	0	1	1	2	1	3	2	1	1	1	1	80	A	A	A
92	1	4	4	3	3	2	2	1	0	0	0	1	1	2	1	2	2	2	1	1	1	80	A	A	A
93	0	3	4	4	4	3	2	0	0	1	0	1	1	1	2	2	2	1	2	1	1	80	A	A	A
91.33333333	0	4	3	4	4	2	2	0	0	1	1	0	1	1	1	2	2	2	1	1	1	100	P	A	A
87	1	3	4	2	2	4	2	0	0	0	0	1	2	1	1	2	2	1	1	1	1	120	A	A	A
87.66666667	1	4	3	3	4	3	2	0	0	0	1	1	1	1	2	2	2	1	2	1	1	130	A	A	A
92.66666667	1	4	4	3	3	3	2	0	0	0	0	1	1	2	1	2	1	2	1	1	1	80	A	A	A
90.33333333	1	4	4	3	4	2	3	1	0	0	1	1	1	1	1	2	2	2	1	1	1	90	A	A	A
83.33333333	0	3	4	5	3	2	3	1	1	1	1	1	2	2	2	2	1	2	1	1	1	80	A	A	A
92	0	4	3	4	4	3	3	1	0	0	0	1	1	1	1	2	2	2	1	1	1	100	P	P	A
84	1	5	3	2	4	4	3	0	0	1	1	1	2	2	1	3	2	2	1	1	1	120	A	A	P
89.66666667	1	5	4	3	2	2	3	0	0	1	0	1	2	1	2	1	2	2	1	1	1	100	A	A	A
95.33333333	1	3	4	3	2	3	2	0	1	0	1	0	1	1	1	2	1	2	2	1	1	70	P	A	A
84.33333333	1	3	2	2	3	3	1	1	0	1	0	1	2	1	1	1	2	2	1	1	1	60	A	A	A
89.33333333	0	4	3	3	3	2	3	1	0	1	0	1	1	1	1	1	2	2	2	1	1	70	A	A	A
90	1	3	4	4	3	2	2	0	0	0	0	1	1	1	2	3	2	2	2	1	1	80	A	A	P
95	1	4	4	3	2	3	3	0	0	1	1	1	2	1	1	2	1	2	1	1	1	100	A	A	A
93.33333333	1	4	4	3	2	3	2	1	0	1	0	1	1	2	1	2	1	2	2	1	1	80	A	A	A
100	2	7	6	6	5	4	3	1	2	2	2	1	2	2	1	2	1	1	1	1	1	240	A	A	A
99.33333333	1	7	6	5	4	5	4	1	2	2	1	1	1	2	1	1	1	1	1	1	1	170	A	A	A
95.66666667	1	6	2	3	4	4	3	1	2	1	1	2	2	2	1	1	1	1	1	1	1	180	A	A	A
97.33333333	1	3	4	4	3	4	3	2	1	1	2	2	1	2	1	1	1	1	1	1	1	80	A	A	A
90	0	5	3	4	3	4	4	1	2	1	1	1	1	2	1	1	1	2	1	1	1	100	A	A	A
96.66666667	1	6	5	6	4	4	3	1	3	2	2	2	1	2	1	1	1	1	1	1	1	180	A	A	A
94.66666667	2	4	5	6	4	4	4	2	2	2	1	1	1	2	1	1	1	1	1	1	1	170	A	P	A
95.66666667	1	3	4	3	4	3	3	1	2	1	1	2	2	3	1	1	2	1	1	1	1	70	A	A	A

97.66666667	1	6	4	5	3	3	4	3	2	2	2	1	3	3	1	1	1	1	1	1	1	140	A	A	A
87.33333333	1	5	4	4	5	4	3	1	3	2	1	2	1	2	1	1	1	1	1	1	1	140	A	A	A
94.66666667	1	6	2	4	4	4	3	3	3	2	1	1	2	2	1	1	1	2	1	1	1	130	A	A	A
97.33333333	1	7	5	3	4	4	3	2	1	1	2	2	3	2	1	1	1	1	1	1	1	190	A	A	A
96.33333333	0	7	4	5	3	3	4	1	2	1	2	1	1	2	1	1	1	1	1	1	1	160	P	A	A
97	0	7	4	4	5	3	3	1	2	1	2	1	2	2	1	1	1	1	1	1	1	160	A	A	A
96.33333333	0	7	3	3	5	4	2	1	2	2	2	1	2	2	1	1	1	1	1	1	1	140	A	A	A
87.66666667	1	6	4	3	5	4	3	3	3	2	1	2	3	2	1	1	1	1	1	1	1	140	A	A	A
95.33333333	1	6	4	4	3	4	3	1	2	2	2	1	1	2	1	1	2	1	1	1	1	120	A	A	A
91	0	5	5	4	5	3	4	3	1	2	2	2	2	2	1	1	1	2	1	1	1	150	A	A	A
96.66666667	1	6	5	5	4	4	3	2	3	2	2	3	3	2	1	1	1	1	1	1	1	180	P	A	A
90.66666667	1	5	3	2	4	5	4	2	2	2	2	2	2	2	1	1	1	1	1	1	1	120	A	A	A
89.33333333	1	7	3	4	3	4	3	2	2	1	1	2	2	2	1	1	1	1	1	1	1	130	A	A	A
95	1	5	4	3	4	3	2	2	3	1	2	2	1	1	1	1	1	1	1	1	1	90	A	A	A
95	0	6	5	4	3	4	3	3	2	2	1	2	1	2	1	1	1	1	1	1	1	140	A	A	A
97	1	5	6	5	4	3	4	1	2	2	2	1	1	2	1	1	2	1	1	1	1	170	A	A	A
98	1	7	4	5	5	5	4	1	2	2	2	1	2	2	1	1	1	2	1	1	1	220	A	A	A